How do we use pathways, like everything that we do, as a tool for learning both to inform physicians of clinical trial opportunities, but also to capture the decisions that are being made on every patient, and to learn from those?

David M. Jackman, MD
Dana-Farber Cancer Institute

You should get measured against the market that you’re in. The variability in those markets is significant.

Terrill Jordan, LLM, JD
Regional Cancer Care Associates

We can really make pathways work for our patients, because that’s who we’re there to serve.

Mishellene McKinney, MHA, RN, OCN
Roswell Park Comprehensive Cancer Center

[Patients are] interested in overall survival and living a better quality of life. There’s a real focus on toxicities of therapy. And that’s where I think precision oncology is so valuable.

Edward R. Arrowsmith, MD
Tennessee Oncology

What are some of the issues that patients are experiencing with respect to their access to care—their inability, perhaps, to access care?

Karen Winkfield, MD, PhD
Meharry-Vanderbilt Alliance

HIGHLIGHTS FROM THE MEETING

• PRACTICES EMBRACING OCM FIND STABILITY THROUGH COVID-19, SP282.

• CANDID CONVERSATIONS WITH PATIENTS KEY TO REDUCING DISPARITIES IN CARE, SP288.

• CITY OF HOPE’S LEVINE HIGHLIGHTS CHALLENGES IN CANCER CARE EQUITY, SP298.

• PAYER AND PROVIDER COLLABORATION A MUST FOR BIOSIMILARS, S299.

• BRINGING THE PATIENT’S VOICE TO CLINICAL PATHWAYS, SP306.

• TEXAS ONCOLOGY’S PATT DISCUSSES EFFECTS OF FEDERAL POLICY ON CANCER CARE, SP314.
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Primary endpoint:**

with mCRPC previously treated with a docetaxel-multicenter study of JEVTANA 25 mg/m² (n=378)

A randomized, open-label, international, treatment in mCRPC after TROPIC Study2 (N=755)

BMS manifested as neutropenia,

**WARNINGS AND PRECAUTIONS**

of normal (ULN)).

Neutropenia: Neutropenic deaths have been reported. Monitor blood counts frequently to determine if initiation of G-CSF and/or dosage modification is needed. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. Caution is recommended in patients with hemoglobin <10 g/dl.

**Increased Toxicities in Elderly Patients:** Patients ≥65 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely.

**Hypersensitivity Reactions:** Severe hypersensitivity reactions can occur. Premedicate all patients with antihistamines, corticosteroids and H2 antagonists prior to JEVTANA. Observe patients closely, especially during the first and second infusions. Discontinue JEVTANA immediately if severe hypersensitivity occurs and treat as indicated.

**Gastrointestinal (GI) Adverse Reactions:** Nausea, vomiting, and severe diarrhea may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials and mortality related to diarrhea has been reported. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Rehydrate and treat with antiemetics and anti-diarrheals as needed. If experiencing grade ≥3 diarrhea, dosage should be modified.

GI hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antplatelet therapy or anticoagulants, and prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding. Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious GI toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.
What’s next... what’s possible.

Discover the possibilities for your metastatic castration-resistant prostate cancer (mCRPC) patients when prescribed JEVTANA early post docetaxel

Prescribed to over 40,000 men†

The efficacy and safety of JEVTANA were evaluated in the TROPIC and PROSELICA trials. Most recently, results from the CARD study were published in the New England Journal of Medicine and presented at 2020 ASCO GU, AUA, and ASCO. Data from the TROPIC and PROSELICA studies are included in the US Prescribing Information for JEVTANA.

CARD Study3 (N=255)

The first comparative, prospective, phase 4 trial evaluating JEVTANA vs abiraterone or enzalutamide

A randomized, open-label, multicenter study of JEVTANA 25 mg/m² vs an androgen receptor (AR)-targeted agent (abiraterone or enzalutamide) in patients with mCRPC who had previously received docetaxel and had disease progression within 12 months on an alternative AR-targeted agent.

Primary endpoint: radiographic progression-free survival

Renal Failure: Cases, including those with fatal outcomes, have been reported. Identify cause and manage aggressively.

Urinary Disorders including Cystitis: Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

Respiratory Disorders:Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection. Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

Use in Patients with Hepatic Impairment: JEVTANA dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 to ≤3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients. Administer JEVTANA 20 mg/m² for mild hepatic impairment. Administer JEVTANA 15 mg/m² for moderate hepatic impairment. Monitor closely.

Embryo-Fetal Toxicity: JEVTANA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA.

ADVERSE REACTIONS (ARs)
The most common all grades adverse reactions and laboratory abnormalities (≥10%) with JEVTANA 20 mg/m² or 25 mg/m² are neutropenia, anemia, leukopenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

DRUG INTERACTIONS
Avoid coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction.

USE IN SPECIFIC POPULATIONS
• Pregnancy: The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the drug-associated risk.
• Lactation: The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of JEVTANA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.
• Females and Males of Reproductive Potential: Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of JEVTANA.

Please see Brief Summary of the full Prescribing Information, including Boxed WARNING, on the following pages.

JEVTANA® (cabazitaxel) injection, for intravenous use

Brief Summary of Prescribing Information

**INDICATIONS AND USAGE**
JEVTANA® is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have progressed after treatment with a hormone-sensitive-containing treatment regimen.

**DOSEAGE AND ADMINISTRATION**

2.1 Preparation

The recommended dose of JEVTANA is based on calculation of the Body Surface Area (BSA), and is 20 mg/m² administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout the treatment cycle.

2.2 Dose Modifications for Adverse Reactions

Patients at a 25 mg/m² dose who require dose reduction may decrease dosage to 20 mg/m². In select patients at the discretion of the treating healthcare provider, a dose of 25 mg/m² can be used in select patients at the discretion of the treating healthcare provider.

**CONTRAINDICATIONS**

JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500/mm³. Primary prophylaxis with G-CSF is recommended if decreased neutrophil counts occur with JEVTANA use. Discontinue JEVTANA if grade 4 neutropenia is sustained for >1 week or is accompanied by infection.

**WARNINGS AND PRECAUTIONS**

5.3 Bone Marrow Suppression

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported.

5.4 Gastrointestinal Adverse Reactions

In PROSELICA, cystitis and radiation cystitis were not observed in patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur in patients who have received prior pelvic radiation for prostate cancer.

5.6 Urinary Disorders Including Cystitis

In PROSELICA, cystitis and radiation cystitis were not observed in patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur in patients who have received prior pelvic radiation for prostate cancer.

5.7 Respiratory Disorders

In PROSELICA, cystitis and radiation cystitis were not observed in patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur in patients who have received prior pelvic radiation for prostate cancer.

5.8 Nerve Pain

In PROSELICA, cystitis and radiation cystitis were not observed in patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur in patients who have received prior pelvic radiation for prostate cancer.

6.1 Clinical Trials Experience

The following serious adverse reactions are discussed in greater detail in another section of this label:

- Bone Marrow Suppression
- Myelosuppression
- Febrile Neutropenia
- Neutropenic Infections
- Hypothyroidism
- Hypercalcemia
- Urinary Adverse Reactions
- Respiratory Adverse Reactions
- Nerve Pain
- Gastrointestinal Adverse Reactions
- Peripheral Edema
- Myocardial Infarction
- Angina
- Arrhythmia
- Pulmonary Edema
- Dyspnea
- Peripheral Neuropathy
- Dextrocardia
- Bone Marrow Suppression
- Myelosuppression
- Febrile Neutropenia
- Neutropenic Infections
- Hypothyroidism
- Hypercalcemia
- Urinary Adverse Reactions
- Respiratory Adverse Reactions
- Nerve Pain
- Gastrointestinal Adverse Reactions
- Peripheral Edema
- Myocardial Infarction
- Angina
- Arrhythmia
- Pulmonary Edema
- Dyspnea
- Peripheral Neuropathy
- Dextrocardia

The table below lists the adverse reactions reported in ≥1% of patients treated with JEVTANA and not listed in other tables in this section carefully before mixing and diluting. JEVTANA requires mixing of the drug and diluent. Do not shake.

<table>
<thead>
<tr>
<th>Toxicity Category</th>
<th>Toxicity</th>
<th>JEVTANA n (%)</th>
<th>Mitoxantrone n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>Arrhythmia ‡</td>
<td>18 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>43 (12%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Arrhythmia ‡</td>
<td>Decreased appetite</td>
<td>76 (13%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>135 (32%)</td>
<td>137 (36%)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>29 (5%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
<td>82 (14%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>24 (4%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>65 (14%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>196 (34%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>226 (40%)</td>
<td>25 (5%)</td>
</tr>
<tr>
<td></td>
<td>Neutropenic infections</td>
<td>190 (31%)</td>
<td>17 (4%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral Edema</td>
<td>34 (9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>38 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral sensory neuropathy</td>
<td>63 (11%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>29 (5%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>Skin and Subcutaneous disorders</td>
<td>66 (12%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>119 (20%)</td>
<td>44 (10%)</td>
</tr>
<tr>
<td></td>
<td>Urinary Adverse Reactions</td>
<td>124 (21%)</td>
<td>25 (4%)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract obstruction</td>
<td>38 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Wound complications</td>
<td>11 (2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

6.3 Reproductive System Adverse Reactions

In PROSELICA, adverse reactions related to secondary sexual characteristics, including changes in libido, were reported in 17% of patients treated with JEVTANA. Increased Toxicities in Elderly Patients

In PROSELICA, patients ≥65 years of age experienced an increased incidence of adverse reactions compared to rates in other trials and may not reflect the rates observed in clinical practice.

6.6 Limited Data

Any Adverse Reaction

The table below lists adverse reactions reported in ≥1% of patients treated with JEVTANA and not listed in other tables in this section carefully before mixing and diluting. JEVTANA requires mixing of the drug and diluent. Do not shake.

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<thead>
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<th>Toxicity Category</th>
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<td>Dyspnea</td>
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<td>4 (1%)</td>
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<td>Fever</td>
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<td>137 (36%)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>29 (5%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
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<td>Hematuria</td>
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<td>11 (2%)</td>
</tr>
<tr>
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<td>Hypercalcemia</td>
<td>24 (4%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>65 (14%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
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<td>11 (3%)</td>
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<tr>
<td></td>
<td>Neutropenia</td>
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<td>25 (5%)</td>
</tr>
<tr>
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<td>Neutropenic infections</td>
<td>190 (31%)</td>
<td>17 (4%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral Edema</td>
<td>34 (9%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>38 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
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<td>1 (0.2%)</td>
</tr>
<tr>
<td></td>
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</tr>
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<td></td>
<td>Urinary tract infection</td>
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<td>Urinary Adverse Reactions</td>
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<tr>
<td></td>
<td>Wound complications</td>
<td>11 (2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>
TROJAN (cabadzol tablet, for intravenous use

The safety of JEVITANA in combination with prednisone was evaluated in 371 patients with metastatic castration-resistant prostate cancer treated in the randomized TROJAN trial, compared to mitoxantrone plus prednisone. Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVITANA-treated patients and 20 (5%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVITANA-treated patients were infections (4%) and renal failure (2%). The majority (4%) of fatal infection-related adverse reactions occurred after a single dose of JEVITANA. Other fatal adverse reactions in JEVITANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥10%) grade 1-4 adverse reactions were anemia, leucopenia, neutropenia, thrombocytopenia, fatigue, nausea, vomiting, constipation, asthma, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysuria, cough, arthralgia, and alopecia. The most common (≥5%) grade 3-4 adverse reactions in patients who received JEVITANA were neutropenia, leucopenia, anemia, febrile neutropenia, diarrhea, fatigue, and anemia.

Treatment discontinuations due to adverse drug reactions occurred in 18% of patients who received JEVITANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEVITANA group were neutropenia and renal failure. Dose reductions were reported in 10% of JEVITANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEVITANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2: Incidence of Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients Receiving JEVITANA in Combination with Prednisone in Treatment of TROPIC

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1-4 n (%)</th>
<th>Grade 3-4 n (%)</th>
<th>Grade 1-4 n (%)</th>
<th>Grade 3-4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>136 (37%)</td>
<td>18 (5%)</td>
<td>102 (27%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>59 (16%)</td>
<td>3 (1%)</td>
<td>39 (11%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>18 (5%)</td>
<td>8 (2%)</td>
<td>10 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>60 (16%)</td>
<td>14 (4%)</td>
<td>45 (12%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>59 (17%)</td>
<td>4 (1%)</td>
<td>31 (9%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>27 (7%)</td>
<td>0</td>
<td>10 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Neuropathy*</td>
<td>50 (13%)</td>
<td>3 (1%)</td>
<td>12 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>41 (11%)</td>
<td>0</td>
<td>15 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (8%)</td>
<td>0</td>
<td>21 (6%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (8%)</td>
<td>0</td>
<td>19 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary Tract Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (17%)</td>
<td>7 (2%)</td>
<td>13 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>35 (9%)</td>
<td>1 (0.3%)</td>
<td>12 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>27 (7%)</td>
<td>0</td>
<td>10 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Neuropathy*</td>
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<td>12 (3%)</td>
<td>3 (1%)</td>
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<td>41 (11%)</td>
<td>0</td>
<td>15 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (8%)</td>
<td>0</td>
<td>21 (6%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (8%)</td>
<td>0</td>
<td>19 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>43 (12%)</td>
<td>4 (1%)</td>
<td>16 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>40 (11%)</td>
<td>0</td>
<td>22 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>37 (10%)</td>
<td>0</td>
<td>18 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (5%)</td>
<td>2 (0.1%)</td>
<td>9 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
| \[*Graded using NCI CTCAE version 3.\]

The median duration of treatment in the TROPIC trial was 6 cycles (range, 1-4 cycles).

Table 3: Incidence of Adverse Reactions in ≥5% of Patients Receiving JEVITANA in Combination with Prednisone in PROSELICA

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1-4 n (%)</th>
<th>Grade 3-4 n (%)</th>
<th>Grade 1-4 n (%)</th>
<th>Grade 3-4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>136 (37%)</td>
<td>18 (5%)</td>
<td>102 (27%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>41 (11%)</td>
<td>0</td>
<td>15 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (8%)</td>
<td>0</td>
<td>21 (6%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (8%)</td>
<td>0</td>
<td>19 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary Tract Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (17%)</td>
<td>7 (2%)</td>
<td>13 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>35 (9%)</td>
<td>1 (0.3%)</td>
<td>12 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>27 (7%)</td>
<td>0</td>
<td>10 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Neuropathy*</td>
<td>50 (13%)</td>
<td>3 (1%)</td>
<td>12 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>41 (11%)</td>
<td>0</td>
<td>15 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (8%)</td>
<td>0</td>
<td>21 (6%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (8%)</td>
<td>0</td>
<td>19 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>43 (12%)</td>
<td>4 (1%)</td>
<td>16 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>40 (11%)</td>
<td>0</td>
<td>22 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>37 (10%)</td>
<td>0</td>
<td>18 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (5%)</td>
<td>2 (0.1%)</td>
<td>9 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

\[*Graded using NCI CTCAE version 4.03.\]

\[Evaluated on adverse event reporting.\]

\[Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and unclassified.\]

\[Includes neupropenic sepsis.\]
In study TROPIC, adverse reactions of hematoma, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥2 hematoma was 5% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematoma were well-balanced between arms and do not account for the increased rate of risers on the JEVTANA arm.

In study PROSELUCA, hematoma of all grades was observed in 18% of patients overall. Hepatic Laboratory Abnormalities

The incidence of grade 3 elevations of AST, increased ALT, and increased bilirubin were each ≤1%.

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because these are reported from a population of unknown size, precise estimates of frequency cannot be made. Gastrointestinal: Gastritis, intestinal obstruction.

Respiratory: Intestinal pneumonia/pneumonitis, intestinal lung disease and acute respiratory distress syndrome. Renal and urinary disorders: Radiation recall hemorrhagic cysts. 7. DRUG INTERACTIONS

7.1 CYP3A inhibitors

Cabazitaxel is primarily metabolized through CYP3A (see Clinical Pharmacology [12.3] in the full prescribing information). Strong CYP3A inhibitors (e.g., rifampicin, rifabutin, rifapentine, ritonavir, saquinavir, telithromycin, voltaren) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% reduction in the JEVTANA dosage (see Dosage and Administration [2.4] and Clinical Pharmacology [12.3] in the full prescribing information).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose (see Data).

Data

Nonclinical data

In an early embryonic developmental toxicity study in rats, cabazitaxel was administered intravenously for 15 days prior to mating through Day 6 of pregnancy, which resulted in an increase in pre-implantation loss at 0.2 mg/kg/day and an increase in early resorptions at ≥0.1 mg/kg/day (approximately 0.06 and 0.02 times the Cmax in patients at the recommended human dose, respectively).

In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and embryo-fetal toxicity consisting of increased pre-implantation loss, embryotoxicity, and fetal death when administered intravenously at a dose of 0.16 mg/kg/day (approximately 0.06 times the Cmax in patients at the recommended human dose). Decreased mean fetal body weight was associated with delays in skeletal ossification was observed at doses ≥0.08 mg/kg. Cabazitaxel crossed the placenta barrier within 24 hours of a single intravenous administration of 0.08 mg/kg to pregnant rats at gestational day 17. A dose of 0.08 mg/kg in rat results in a Cmax approximately 0.02 times that observed in patients at the recommended human dose. Administration of cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures.

8.2 Lactation

Risk Summary

The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of cabazitaxel in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats (see Data).

Data

Nonclinical data

In a milk excretion study, radioactivity related to cabazitaxel was detected in the stomachs of nursing pups within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the Cmax in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

8.3 Females and Males of Reproductive Potential

Contraception

None

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of JEVTANA (see Use in Specific Populations [8.1]).

Infertility

None

Based on animal toxicology studies, JEVTANA may impair human fertility in males of reproductive potential (see Nonclinical Toxicology [13.1] in the full prescribing information).

8.4 Pediatric Use

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

JEVTANA was evaluated in 39 pediatric patients (ages 9 to 18 years) receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m² intravenously over 1 hour on Day 1 of a 21 day cycle in pediatric patients with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One patient had a partial response among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events such as bone marrow suppression and gastrointestinal disorders. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearance by body surface area was comparable to those in adults.

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with JEVTANA over the three-weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥65 years of age and younger patients. Elderly patients ≥65 years of age may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients (see Warnings and Precautions [5.2]). The incidence of grade 3–4 neutropenia and thrombocytopenia were higher in patients who were 65 years of age or greater compared to younger patients. The following grade 1–4 adverse reactions were reported at rates ≥5% higher in patients 65 years of age or older compared to younger patients: fatigue (40% vs 30%), neutropenia (27% vs 19%), and thrombocytopenia (4% vs 1%). One patient had a partial response among the 9 patients with ependymoma.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearance by body surface area was comparable to those in adults.

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance Clcrea < 15 mL/min/1.73 m²) should be monitored carefully during treatment (see Clinical Pharmacology [12.3] in the full prescribing information).

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 to ≤3.0 × ULN) should have JEVTANA dose of 20 mg/m². Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety (see Clinical Pharmacology [12.3] in the full prescribing information). The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to ≤3.0 × ULN and AST = any) was 15 mg/m², however, the efficacy at this dose level was unknown. JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) (see Contraindications [4]).
Sharing Payment Reform Progress in a Pandemic

WHEN WE PLANNED THE 2020 EDITION of Patient-Centered Oncology Care®, we hoped to bring our annual meeting to Nashville, Tennessee, the headquarters for the OneOncology community oncology partnership and a focal point for so much positive change in payment reform. But the coronavirus disease 2019 (COVID-19) pandemic called for a change of plans, and on September 25, 2020, we presented the first-ever virtual meeting to hundreds of online followers. Our cochairs, Joseph Alvaram, MD, and Kashyap Patel, MD, expertly guided panelists and attendees through a riveting day of discussion, with each session followed by virtual sharing in a question-and-answer room. The feedback that day—and since—has been tremendous. We heard from many stakeholders, including payers, who would not have been able to join us in person. And their verdict? As challenging as it is during the time of COVID-19, moving forward with payment reform is essential. Those practices that had already embraced the movement toward rewarding quality, toward continually reaching out to patients, and toward revenue streams not solely tied to administrative functions have learned that cling to the old model call for better management of chronic conditions and a holistic approach to care. Since March, these practices have learned that cling to the old model at their peril, for the high-touch operations are not only better for patients but also offer access to new revenue streams that can keep practices afloat.

We learned, too, how COVID-19 has shone a bright light on the disparities in health care, which affect who gets screened and who gains access to the best cancer care once a diagnosis is made. Closing the equity gap will be unfinished business for years to come. Unfortunately, as we learned in a session led by Dr Patel, too many oncologists have been content with the old buy-and-bill model; too many have ignored reimbursement opportunities offered by CMS that call for better management of chronic conditions and access to new revenue streams that can keep practices afloat.

The explosion in therapeutic advances, driven by our knowledge of genomics, must necessarily be integrated with the timing of surgical care, including payers, who would not have been able to present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care. The focus on quality will be more important than ever as the pandemic reaches a new phase. We know that many patients skipped screenings in the early months, and this created downstream effects as patients are now being diagnosed with later-stage cancers. The next phase of quality measurement and payment reform must focus on better connections between screening in primary care and referrals to the oncologist, and among the treatments provided by the medical, radiation, and surgical oncology specialists.

We don't know all that the next year will bring, but we do know that this groundbreaking version of PCOC will not be our last effort in a virtual format. We look forward to more ideas for our 2021 meeting. Thank you for reading.

Sincerely,
Mike Hennessy, Sr
Chairman and Founder

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INQOVI® (decitabine and cedazuridine) tablets is the first and only once-daily oral HMA treatment for adult patients with MDS, including CMML¹

WITH NEW INQOVI, PATIENTS CAN NOW TAKE THEIR MEDICATION AT HOME, REDUCING THE NEED FOR FREQUENT OFFICE VISITS TO RECEIVE INTRAVENOUS THERAPY.¹

The recommended dose of INQOVI is one tablet taken orally once daily on Day 1 through Day 5 of each 28-day cycle for minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles.¹

INDICATIONS
INQOVI is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.¹

Please see Important Safety Information on the next page and brief summary of Prescribing Information on the following pages.

HMA=hypomethylating agent; CMML=chronic myelomonocytic leukemia; MDS=myelodysplastic syndromes

TO LEARN MORE ABOUT INQOVI, VISIT INQOVI.COM
IMPORTANT SAFETY INFORMATION AND INDICATIONS

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Myelosuppression: Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%.

Fatal and serious infectious complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1%.

Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended.

Embryo-Fetal Toxicity: INQOVI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise patients to use effective contraception during treatment and for 6 months (females) or 3 months (males) after last dose.

ADVERSE REACTIONS

Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

The most common adverse reactions (≥ 20%) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with INQOVI and for at least 2 weeks after the last dose.

Renal Impairment: No dosage modification of INQOVI is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions. INQOVI has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (ESRD: CLcr < 15 mL/min).

INDICATIONS

INQOVI is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

Please see brief summary of Prescribing Information on the following pages.

INQOVI® (decitabine and cedazuridine) tablets, for oral use.

Prescription Only.

Initial U.S. Approval: 2020

Brief Summary of Prescribing Information
For complete Prescribing Information, consult official package insert.

1 INDICATIONS AND USAGE
INQOVI is indicated for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 72% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients.

Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

Fatal and serious infections complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1% [see Adverse Reactions (6.1) in the full Prescribing Information].

Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended [see Dosage and Administration (2.2) in the full Prescribing Information].

5.2 Embryo-Fetal Toxicity
Based on findings from human data, animal studies, and its mechanism of action, INQOVI can cause fetal harm when administered to a pregnant woman. In nonclinical studies with decitabine in mice and rats, decitabine was teratogenic, fetotoxic, and embryocidal at doses less than the recommended human dose.

Advising pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with INQOVI and for 3 months after the last dose [see Use in Specific Populations (8.1-8.13) in the full Prescribing Information].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression [see Warnings and Precautions (5.1) in the full Prescribing Information]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia
The safety of INQOVI was evaluated in a pooled safety population that includes patients enrolled in Study ASTX727-01-B and Study ASTX727-02 [see Clinical Studies (14) in the full Prescribing Information].

Patients were randomized to receive INQOVI (35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 in Cycle 1 and decitabine 20 mg/m² intravenously on Days 1 through 5 in Cycle 2, or the reverse sequence, and then INQOVI (35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 of each 28-day cycle in Cycles 3 and beyond. Patients were allowed to have one prior cycle of decitabine or azacitidine and there was no limit for body weight or surface area. Among the patients who received INQOVI, 61% of patients were exposed for 6 months or longer and 24% were exposed to INQOVI for greater than 1 year.

Serious adverse reactions occurred in 88% of patients who received INQOVI. Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions occurred in 6% of patients. These included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received INQOVI. The most frequent adverse reactions resulting in permanent discontinuation were febrile neutropenia (1%) and pneumonia (1%).

Dose interruptions due to an adverse reaction occurred in 41% of patients who received INQOVI. Adverse reactions requiring dosage interruptions in > 5% of patients who received INQOVI included neutropenia (18%), febrile neutropenia (8%), thrombocytopenia (6%), and anemia (5%).

Dose reductions due to an adverse reaction occurred in 19% of patients who received INQOVI. Adverse reactions requiring dosage reductions in > 2% of patients who received INQOVI included neutropenia (12%), anemia (3%), and thrombocytopenia (3%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and transaminase increased. The most common Grade 3 or 4 laboratory abnormalities (≥ 50%) were leukocytes decreased, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.

Table 2 summarizes the adverse reactions in the pooled safety population.

Table 2: Adverse Reactions (≥ 10%) in Patients Who Received INQOVI in Pooled Safety Population

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>INQOVI Cycle 1 N=107</th>
<th>Intravenous Decitabine Cycle 1 N=106</th>
<th>INQOVI All Cycles N=208</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>24</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>10</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
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<td>0</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Constipation</td>
<td>20</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
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<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>11</td>
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<tr>
<td>Transaminase increased</td>
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<td>3</td>
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<tr>
<td>Abdominal pain</td>
<td>9</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<td></td>
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</tr>
<tr>
<td>Myalgia</td>
<td>9</td>
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<td>1</td>
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<tr>
<td>Arthralgia</td>
<td>9</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Cough</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Blood &amp; lymphatic system disorders</td>
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<tr>
<td>Neutropenia</td>
<td>10</td>
<td>10</td>
<td>13</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<tr>
<td>Rash</td>
<td>12</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

(continued)
Table 2: Adverse Reactions (≥ 10%) in Patients Who Received INQOVI in Pooled Safety Population

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>INQOVI Cycle 1 N=107</th>
<th>Intravenous Decitabine Cycle 1 N=106</th>
<th>INQOVI + Intravenous Decitabine All Cycles N=208</th>
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<tbody>
<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Dizziness</td>
<td>16 0 1 11 0 33 2</td>
<td>12 0 1 11 0 30 0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22 0 1 11 0 30 0</td>
<td>12 0 1 11 0 30 0</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4 0 1 11 0 13 0</td>
<td>12 0 1 11 0 30 0</td>
<td></td>
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<tr>
<td>Metabolism and nutritional disorders</td>
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</tr>
<tr>
<td>Decreased appetite</td>
<td>10 1 1 6 0 24 2</td>
<td>12 0 1 6 0 20 2</td>
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</tr>
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<td>Infections and infestations</td>
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<td>12 0 3 0 20 1</td>
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<tr>
<td>Pneumonia</td>
<td>7 7 7 5 21 15</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>6 6 2 1 14 11</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>4 1 3 2 12 5</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>9 0 1 8 0 18 0</td>
<td>12 0 1 8 0 10 1</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>5 0 1 3 0 10 1</td>
<td>12 0 1 3 0 8 1</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>4 0 1 0 12 1</td>
<td>12 0 1 0 8 1</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 0 2 12 0 12 0 5</td>
<td>12 0 2 12 0 8 1</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 0 6 1 11 2</td>
<td>12 0 6 1 10 2</td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 0 2 0 11 1</td>
<td>12 0 2 0 10 1</td>
<td></td>
</tr>
</tbody>
</table>

Includes adverse reactions that occurred during all cycles, including during treatment with 1 cycle of intravenous decitabine.

1 Includes fatigue, asthenia, and lethargy.
2 Includes confusion, epistaxis, petechiae, hematuria, coenujunctival hemorrhage, mouth hemorrhage, purpura, angina bullosa hemorrhagica, gingival bleeding, hemoptysis, hemoptysis, epistaxis, eye confusion, hemorrhagic diathesis, increased tendency to bruise, papular hemorrhage, and papular hemorrhage.
3 Includes edema peripheral, peripheral swelling, swelling face, fluid overload, localized edema, face edema, edema, eye swelling, eyelid edema, edema fluid, retention, edema swelling, scleral edema, serocel edema, scrotal swelling, and swelling.
4 Includes constipation and feces.
5 Includes oropharyngeal pain, stomatitis, mouth ulceration, proctalgia, oral pain, gingivitis, oral disorder, gingival pain, colitis, glossodynia, mouth swelling, pharyngitis, proctitis, duodenum, enteritis, gingival discomfort, gingival swelling, lip disorder, lip ulceration, mucosal ulceration, nasal ulcer, noninfective gingivitis, oral mucosal blistering, oral mucosal erythema, pharyngal erythema, pharyngeal ulceration, tongue ulceration, and vulvitis.
6 Includes myalgia, pain in extremity, muscle spasms, pain, musculoskeletal pain, non-cardiac chest pain, muscular weakness, musculoskeletal chest pain, flank pain, musculoskeletal stiffness, muscle strain, and musculoskeletal discomfort.

Table 3: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who Received INQOVI in Pooled Safety Population

<table>
<thead>
<tr>
<th>Lab Abnormality</th>
<th>INQOVI Cycle 1</th>
<th>Intravenous Decitabine Cycle 1</th>
<th>INQOVI + Intravenous Decitabine All Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>58 1 3 10 0 71 55</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>19 0 11 0 54 7</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>22 1 20 0 45 2</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphate increased</td>
<td>22 1 12 0 42 0.5</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>14 0 17 0 40 1</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>9 2 6 0 30 4</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>16 0 12 0 30 2</td>
<td>12 0 3 0 20 1</td>
<td></td>
</tr>
</tbody>
</table>

Includes any lab abnormalities that worsened by one or more grades.

The denominator used to calculate the rate varied from 103 to 107 for INQOVI Cycle 1, from 102 to 106 for Intravenous Decitabine Cycle and from 203 to 208 for INQOVI All Cycles based on the number of patients with a baseline value and at least one post-treatment value.
6.2 Postmarketing Experience
The following adverse reactions have been identified through postapproval use of intravenous decitabine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Differentiation syndrome
Respiratory, Thoracic and Mediastinal Disorders: Interstitial lung disease
7 DRUG INTERACTIONS
7.1 Effects of INQOVI on Other Drugs
Drugs Metabolized by Cytochrome P450
Cedazuridine is an inhibitor of the cytidine deaminase (CDA) enzyme.
Co-administration of INQOVI with drugs that are metabolized by CDA may result in increased systemic exposure with potential for increased toxicity of these drugs [see Clinical Pharmacology (12.3) in the full Prescribing Information]. Avoid coadministration of INQOVI with drugs that are metabolized by CDA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on findings from human data, animal studies, and its mechanism of action [see Clinical Pharmacology (12.1) in the full Prescribing Information], INQOVI can cause fetal harm when administered to a pregnant woman. A single published case report of intravenous decitabine use throughout the first trimester during pregnancy describes adverse developmental outcomes, including major birth defects (structural abnormalities). In animal reproduction studies, intravenous administration of decitabine to pregnant mice and rats during organogenesis at doses approximately 7% of the recommended human dose on a body surface area (mg/m²) basis caused adverse developmental outcomes, including increased embryo-fetal mortality, alterations to growth, and structural abnormalities [see Data]. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Human Data
There are no available data on INQOVI use in pregnant women. A single published case report of intravenous decitabine pregnancy exposure in a 39-year-old woman with a hematologic malignancy described multiple structural abnormalities after 6 cycles of therapy in the 13th week of gestation. These abnormalities included holoprosencephaly, absence of nasal bone, mid-facial deformity, cleft lip and palate, polydactyly, and rocker-bottom feet. The pregnancy was terminated.

Animal Data
No reproductive or developmental toxicity studies have been conducted with INQOVI or cedazuridine.
In utero exposure to decitabine causes temporal-related defects in the rat and/or mouse, which include growth suppression, exencephaly, defective skull bones, rib/intercostal defects, phocomelia, digit defects, micrognathia, gastrochisis, and micromelia. Decitabine inhibits proliferation and increases apoptosis of neural progenitor cells of the fetal central nervous system (CNS) and induces palatal clefting in the developing murine fetus. Studies in mice have also shown that decitabine administration during osteoblastogenesis (Day 10 of gestation) induces bone loss in offspring. In mice exposed to single intraperitoneal decitabine injections (0.9 and 3.0 mg/m², approximately 2% and 7% of the recommended daily clinical dose, respectively) over gestation Days 8, 9, 10 or 11, no maternal toxicity was observed, but reduced fetal survival was observed after injection at 3 mg/m² and decreased fetal weight was observed at both dose levels. The 3 mg/m² dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae and ribs, cleft palate, vertebral defects, hind-limb defects, and digital defects of fore- and hind-limbs.
In rats given a single intraperitoneal injection of 2.4, 3.6 or 6 mg/m² decitabine (approximately 5, 8, or 13% the daily recommended clinical dose, respectively) on gestation Days 9-12, no maternal toxicity was observed. No live fetuses were seen at any dose when decitabine was injected on gestation Day 9. A significant decrease in fetal survival and reduced fetal weight at doses greater than 3.6 mg/m² was seen when decitabine was given on gestation Day 10. Increased incidences of vertebral and rib anomalies were seen at all dose levels, and induction of exophthalmia, exencephaly, and cleft palate were observed at 6.0 mg/m². Increased incidence of foredigit defects was seen in fetuses at doses greater than 3.6 mg/m². Reduced size and ossification of long bones of the fore-limb and hind-limb were noted at 6 mg/m².
The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m² intraperitoneal injection (approximately 7% the recommended daily clinical dose) on Day 10 of gestation. Body weights of males and females exposed in utero to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed in utero were mated to untreated males. Unrelated females mated to males exposed in utero showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). Follow up studies indicated that treatment of pregnant mice with decitabine on gestation Day 10 was associated with a reduced pregnancy rate resulting from effects on sperm production in the F1-generation.

8.2 Lactation
Risk Summary
There are no data on the presence of cedazuridine, decitabine, or their metabolites in human milk or on their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with INQOVI and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential
INQOVI can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1) in the full Prescribing Information].

Infertility
Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose. Males

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose.

8.4 Pediatric Use
The safety and effectiveness of INQOVI have not been established in pediatric patients.

8.5 Geriatric Use
Of the 208 patients in clinical studies who received INQOVI, 75% were age 65 years and older, while 36% were age 75 years and older. No overall differences in safety or effectiveness were observed between patients age 65 years and older, 75 years and older, and younger patients.

8.6 Renal Impairment
No dosage modification of INQOVI is recommended for patients with mild or moderate renal impairment (creatinine clearance [ClCr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (ClCr 30 to 59 mL/min) frequently for adverse reactions. INQOVI has not been studied in patients with severe renal impairment (ClCr 15 to 29 mL/min) or end-stage renal disease (ESRD: ClCr <15 mL/min). [see Clinical Pharmacology (12.3) in the full Prescribing Information].

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression
Advise patients of the risk of myelosuppression and to report any symptoms of fever, infection, anemia, or bleeding to their healthcare provider as soon as possible. Advise patients for the need for laboratory monitoring [see Warnings and Precautions (5.1) in the full Prescribing Information].

Embryo-Fetal Toxicity
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.1) Use in Specific Populations (8.1) in the full Prescribing Information].
Advise females of reproductive potential to use effective contraception during treatment with INQOVI and for 6 months after the last dose [see Use in Specific Populations (8.3) in the full Prescribing Information].

Advise males with female partners of reproductive potential to use effective contraception during treatment with INQOVI and for 3 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) in the full Prescribing Information].

Lactation

Advise women not to breastfeed during treatment with INQOVI and for 2 weeks after the last dose [see Use in Specific Populations (8.2) in the full Prescribing Information].

Administration

Advise patients to take INQOVI at approximately the same time each day on an empty stomach. Instruct patients to avoid eating for at least 2 hours before and 2 hours after taking INQOVI. Advise patients on what to do when a dose is missed or vomited [see Dosage and Administration (2.2) in the full Prescribing Information].

Full Prescribing Information is available at www.inqovi.com/pi or by calling 1-844-824-4648.

© TAIHO ONCOLOGY, INC. 07/2020
Collaboration is the name of the game in cancer care today, whether it’s taking the time for chronic care management or implementing alternative payment models that call for navigators to help patients through the care journey.
DRIVEN TO FULFILL THE PROMISE OF BIOSIMILARS—THE PFIZER WAY

The Pfizer Promise is simple:
To help you provide patients with more treatment options while delivering the largest portfolio of potentially cost-saving biosimilars.1-3

Breadth of offerings
Pfizer has the largest portfolio of oncology biosimilars on the market, including both cancer therapies and supportive care products, to give patients more treatment options.2,3

Quality focused
Pfizer oncology biosimilars are all produced to meet the same high-quality standards as its biologics—using the same robust protocols for monitoring quality throughout every stage of the manufacturing process.4

Manufacturing and supply experience
Pfizer leverages more than 30 years of state-of-the-art manufacturing and supply-chain experience in biologics to reliably deliver biosimilars to patients.4

To learn more about Pfizer’s oncology biosimilars, visit us online at PfizerBiosimilars.com

# AGENDA & FACULTY

## AGENDA

**Friday, September 25, 2020**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 to 8:45 AM</td>
<td>Welcome and Keynote Presentation: Oncology Care Model Experiences during COVID</td>
</tr>
<tr>
<td></td>
<td>Alexandra Chong, PhD</td>
</tr>
<tr>
<td>8:45 to 9:30 AM</td>
<td>Advancing Chronic Care Management</td>
</tr>
<tr>
<td></td>
<td>Johnetta Blakely, MD, MBA</td>
</tr>
<tr>
<td>9:30 to 10:15 AM</td>
<td>Impacting Health Care Disparities in Oncology</td>
</tr>
<tr>
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<td>Emeline Aviku, MD, MBA</td>
</tr>
<tr>
<td>10:15 to 10:35 AM</td>
<td>Break</td>
</tr>
<tr>
<td>10:35 to 11:05 AM</td>
<td>Featured Speaker: Optimizing the Impact of the Cancer Revolution</td>
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<tr>
<td></td>
<td>Harlan Levine, MD</td>
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<tr>
<td>11:05 to 12:10 PM</td>
<td>Oncology Care First: Policy and Treatment Implications</td>
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<tr>
<td></td>
<td>Mariam Alboustanii, RPh</td>
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<td></td>
<td>Aaron Lyss, MBA</td>
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<td>Terrill Jordan, LLM, JD</td>
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<td>Randall A. Oyer, MD</td>
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<td>12:10 to 12:40 PM</td>
<td>Break</td>
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<tr>
<td>12:40 to 12:55 PM</td>
<td>Featured Speaker: Federal Cancer Policy</td>
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<td>Debra Fatt, MD, PhD, MBA</td>
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<td>12:55 to 1:40 PM</td>
<td>PBMs and Access to Pharmacy Care in a Value-based Care Environment</td>
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<tr>
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<td>Ray Bailey, BPharm, RPh</td>
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<td></td>
<td>Denise Giambalvo, MSHRM</td>
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<td></td>
<td>Antonio Caccia</td>
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<td>Jonathan E. Levitt, JD</td>
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<tr>
<td>1:40 to 2:25 PM</td>
<td>Precision Health and Value-based Care</td>
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<td></td>
<td>Edward R. Arrowsmith, MD</td>
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<td>Lee Schwartzberg, MD, FACP</td>
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<td>David Joseph Debono, MD</td>
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<tr>
<td>2:25 to 2:45 PM</td>
<td>Break</td>
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<tr>
<td>2:45 to 3:30 PM</td>
<td>Advancing Biosimilars: Future Management</td>
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<td></td>
<td>Kannan Abdallah, PharmD</td>
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<td></td>
<td>Bhavesh Shah, RPh, BCOP</td>
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<td></td>
<td>Sean McGowan, MBA</td>
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<tr>
<td>3:30 to 4:15 PM</td>
<td>Clinical Pathways</td>
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<td></td>
<td>Kerin Adelson, MD</td>
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<td>David M. Jackman, MD</td>
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<td></td>
<td>Karen Fields, MD</td>
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<tr>
<td></td>
<td>Mishellene McKinney, MHA, RN, OCN</td>
</tr>
<tr>
<td>4:15 to 4:30 PM</td>
<td>Closing Remarks</td>
</tr>
</tbody>
</table>

## COCHAIRS

**Joseph Alvarnas, MD**  
Vice President of Government Affairs and Senior Medical Director for Employer Strategy  
Associate Clinical Professor, Department of Hematology & Hematopoietic Cell Transplantation  
City of Hope  
Duarte, CA

Joseph Alvarnas, MD, attended medical school at the University of California, San Francisco. He completed internal medicine training and fellowships in hematology and hematopoietic cell transplantation at Stanford University Medical Center. He helped found the City of Hope-Banner Bone Marrow Transplant Program and later served as director of the Hematopoietic Stem Cell Processing Laboratory and chair of the Quality Committee for the transplant program. Today, he is a clinical professor in the Department of Hematology and Hematopoietic Cell Transplantation at City of Hope, where he also serves as the institution’s vice president of Government Affairs and senior medical director for Employer Strategy. Dr Alvarnas served as the national cochair for 2 Blood and Marrow Transplant Clinical Trials Network clinical trials studying stem cell transplantation in patients infected with HIV. He serves on the American Society of Hematology (ASH) Committee on Practice and as an ASH liaison to the Committee on Quality. He is editor-in-chief of Evidence-Based Oncology™, a publication of The American Journal of Managed Care®.

**Kashyap Patel, MD**  
Medical Director, Blue Cross Blue Shield of South Carolina  
CEO Carolina Blood and Cancer Care Associates  
Rock Hill, SC

Kashyap Patel, MD, is the CEO of Carolina Blood and Cancer Care Associates, based in Rock Hill, South Carolina, and was recently named a medical director for Blue Cross Blue Shield of South Carolina. Patel is a board-certified hematologist and oncologist who is the current vice president of the Community Oncology Alliance and a trustee of the Association of Community Cancer Centers. He is recognized as one of the nation’s experts in implementing value-based payment models in the community oncology practice through local partnerships and an emphasis on palliative care. A graduate of St. Xavier’s College, Patel received his medical degree at Thomas Jefferson University. He has served as an independent contractor for Palmetto GBA and a medical director for the International Oncology Network. The associate editor of Evidence-Based Oncology™, Patel is also the author of the recently published book, Between Life and Death: From Despair to Hope.

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**RENUKA TIPIRNENI, MD, MSc, IS NAMED RECIPIENT OF THE 2020 SEEMA S. SONNAD EMERGING LEADER IN MANAGED CARE RESEARCH AWARD**

The American Journal of Managed Care® presented Renuka Tipirneni, MD, MSc, of the University of Michigan with the 2020 Seema S. Sonnad Emerging Leader in Managed Care Research Award during the 9th annual Patient-Centered Oncology Care® 2020 conference, held virtually on September 25, 2020.

“Dr Tipirneni is an outstanding leader and embodies the values and qualities we look for when selecting the Seema S. Sonnad Emerging Leader in Managed Care Research Award winner,” said Mike Heinnessy Jr, president and CEO of MJH Life Sciences®, parent company of AJMC®. “Her extensive background and passion for health reform, Medicaid policy, healthy aging and social determinants of health make her truly deserving of this award.”

Tipirneni is an assistant professor in the University of Michigan department of internal medicine, divisions of general medicine and hospital medicine, and at the Institute for Healthcare Policy & Innovation. Her research focuses on investigating how health reform policies and programs affect patients with low socioeconomic status, older patients and other vulnerable populations.

Currently, Tipirneni’s work includes examinations of Medicaid policy such as work requirements, integration of behavioral and physical health care, and assessments of social determinants of health in clinical practice. She has evaluated the Affordable Care Act, Michigan’s Medicaid expansion, and other state and federal policies. Tipirneni is a recipient of a K08 career development award from the National Institute on Aging for examining the impact of coverage expansions on adults near retirement, and she received the Grace H. Elta MD Department of Internal Medicine Early Career Endowment Award in 2018.

“I am humbled to receive this award from AJMC® that honors the legacy of Seema Sonnad. I strive to carry forward her legacy by continuing to translate research into health policy and mentor the next generation of diverse leaders in health insurance and managed care policy,” said Tipirneni.

This award was established in honor of Seema S. Sonnad, PhD, the former associate editor of AJMC®, who died in June 2015. Sonnad served as a mentor to many young researchers and was an advocate for the creation of an award that recognizes and encourages early career achievements in the field of managed care.
THE ONLY ALL-ORAL PROTEASOME INHIBITOR-BASED REGIMEN FOR THE TREATMENT OF MULTIPLE MYELOMA

Patients with multiple myeloma have a 7-fold increased risk of developing bacterial and viral infections and a 6-fold increased risk of infection-related deaths, compared with matched controls.¹

---

The immune system of patients with multiple myeloma is compromised²

Patients with multiple myeloma are frequently elderly and often have age-related co-morbidities³

---

All-oral regimens may provide the following advantages over IV regimens in some patients with multiple myeloma.

**Decrease Clinic Visits**
Oral treatments may allow patients to reduce the number of clinic visits for drug administration in comparison with IV treatment⁴

**Decrease Administration Costs**
IV administration of anticancer drugs places various financial burdens on the healthcare system, evident especially in the indirect costs associated with drug administration of IV medications⁵

**Patient Preferences**
Ability to receive treatment at home is one of the most frequently reported factors associated with patient preference⁴ ⁶

---

Ixazomib (NINLARO) in combination with lenalidomide and dexamethasone is the only Category 1, preferred all-oral regimen for patients with previously treated multiple myeloma, according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)⁷

---

Allow immediate access to NINLARO, an all-oral proteasome inhibitor-based regimen that can be taken at home, for all members with multiple myeloma that have received at least one prior therapy.

---

For more information on the all-oral NINLARO regimen, contact your Takeda Oncology account manager.

---

**INDICATION**
NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

---

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**  
- **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.

Please see NINLARO (ixazomib) Important Safety Information continued on back page.
IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

• **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

• **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

• **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

• **Cutaneous Reactions**: Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.

• **Thrombotic Microangiopathy**: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

• **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.

• **Embryo-fetal Toxicity**: NINLARO can cause fetal harm. Women should be advised of the potential risk to a fetus, to avoid becoming pregnant, and to use contraception during treatment and for an additional 90 days after the final dose of NINLARO. Women using hormonal contraceptives should also use a barrier method of contraception.

ADVERSE REACTIONS

The most common adverse reactions (> 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

SPECIAL POPULATIONS

• **Hepatic Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.

• **Renal Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

• **Lactation**: Advise nursing women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

Please see accompanying NINLARO® (ixazomib) full Prescribing Information.

5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in both regimens in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm³ during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5000/mm³ during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs). The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen.

Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting, have been reported with NINLARO, occasionally requiring use of anti diarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the NINLARO regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (6% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or severe adverse reactions. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 25% and 18% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the NINLARO regimen and 13% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 4% in the placebo regimen). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 19% of patients in the NINLARO regimen and 11% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (10% in the NINLARO regimen and 7% in the placebo regimen) or Grade 2 (6% in the NINLARO regimen and 3% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

5.6 Thrombotic Microangiopathy: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uraemic syndrome (TTP/HUS), have been reported in patients who received NINLARO. NINLARO should be discontinued in patients with TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of restarting NINLARO therapy in patients previously experiencing TTP/HUS is not known.

5.7 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatitis, cholestatic, and hepatocellular injury have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using NINLARO. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential that they must use effective contraception during treatment with NINLARO and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception.

6 ADVERSE REACTIONS

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

- Thrombocytopenia [see Warnings and Precautions (5.1)]
- Gastrointestinal Toxicities [see Warnings and Precautions (5.2)]
- Peripheral Neuropathy [see Warnings and Precautions (5.3)]
- Peripheral Edema [see Warnings and Precautions (5.4)]
- Cutaneous Reactions [see Warnings and Precautions (5.5)]
- Thrombotic Microangiopathy [see Warnings and Precautions (5.6)]
- Hepatotoxicity [see Warnings and Precautions (5.7)]

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 in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360).

The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in > 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade 3 N (%)</td>
<td>Grade 4 N (%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>69 (19)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathes*</td>
<td>100 (28)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (42)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>122 (34)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>92 (26)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>79 (22)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>68 (19)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>74 (21)</td>
<td>2 (&lt; 1)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>91 (25)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.

*Represents a pooling of preferred terms

(Continued on next page)
8.5 Geriatric Use: The safety and effectiveness of NINLARO in patients 65 years of age and older have not been established. Because of impaired renal function that increases exposure of NINLARO, use with caution and consider a reduced dose of NINLARO in patients with renal impairment.

8.6 Hepatic Impairment: Patients with moderate to severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: There is no known specific antidote for NINLARO overdose. In the event of an overdose, monitor the patient for adverse reactions and provide appropriate supportive care.

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions
- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsules whole with water. The capsule should not be crushed, chewed, or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥ 72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising [see Warnings and Precautions (5.1)].

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their physician if these adverse reactions persist [see Warnings and Precautions (5.2)].

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs [see Warnings and Precautions (5.3)].

Peripheral Edema: Advise patients to contact their physicians if they experience unusual swelling of their extremities or weight gain due to swelling [see Warnings and Precautions (5.4)].

Cutaneous Reactions: Advise patients to contact their physicians if they experience new or worsening rash [see Warnings and Precautions (5.5)].

Thrombotic Microangiopathy: Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur [see Warnings and Precautions (5.6)].

Hepatotoxicity: Advise patients to contact their physicians if they experience jaundice or right upper quadrant abdominal pain [see Warnings and Precautions (5.7)].

Other Adverse Reactions: Advise patients to contact their physicians if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura [see Adverse Reactions (6.1)].

Pregnancy: Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with NINLARO and for 90 days following the last dose.

Breastfeeding: Advise women not to breastfeed during treatment with NINLARO and for 90 days following treatment. Dexamethasone is known to be excreted in human milk. The effects of the drug on the nursing infant are unknown, advise nursing women not to breastfeed during treatment with NINLARO. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20%, respectively.

Please see full Prescribing Information for NINLARO at NINLAROhcp.com.
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FOR ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

BRUKINSA

STAYS ON, SO

BTK

STAYS OFF

100%, 24-hour inhibition of BTK was maintained in peripheral blood when taken as 160 mg twice a day or 320 mg once a day.¹²

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemotherax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy. Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunist infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred. Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman.

¹The clinical significance of 100% occupancy has not been established.

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BRUKINSA™ (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**INDICATION**
BRUKINSA™ is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**REFERENCES**

Please see Brief Summary of full Prescribing Information on the following pages.
EBO_12_2020_PDCDC_Beigene_Brukinsa.indd   280
[95x80]Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet countFOR BRUKINSA™  (zanubrutinib)

5.2 Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hemopathic malignances treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematoma, and hemotoma have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 55% of patients treated with BRUKINSA monotherapy. Bleeding events have occurred in patients with and without concomitant antithplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antithplatelet or anticoagulant medications may further increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias
Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac factors, hyperension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

6. Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

6. ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage [see Warnings and Precautions (5.1)]
- Infections [see Warnings and Precautions (5.2)]
- Cytopenias [see Warnings and Precautions (5.3)]
- Second Primary Malignancies [see Warnings and Precautions (5.4)]
- Cardiac Arrythmias [see Warnings and Precautions (5.5)]

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 in the clinical trials of another drug and may not reflect the rates observed in practice. The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 320 mg once daily in 42 patients in clinical trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year.

In this pooled safety population, the most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (35%), hemoglobin decreased (28%), rash (25%), bruising (23%), diarrhea (23%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)
The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03320087] and BGB-3111-AU-003 [NCT02343120] [see Clinical Studies (14.2)]. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count > 75% x 10^9/L, and an absolute neutrophil count > 1 x 10^9/L, and an absolute neutrophil count ≥ 1 x 10^9/L, independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L, and an absolute neutrophil count > 1 x 10^9/L, independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a Clcr ≥ 30 mL/min. Both trials excluded patients with prior allogenic hematopoetic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serological evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year.

Fetal trials within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fetal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient. Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Percent of Patients (N=118)</th>
<th>All Grades %</th>
<th>Grade 3 or Higher %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia and Neutrophil count decreased</td>
<td>38</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia and Platelet count decreased</td>
<td>27</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopenia and White blood count decreased</td>
<td>25</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia and Hemoglobin decreased</td>
<td>14</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>15</td>
<td>10</td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>36</td>
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<td></td>
<td>Bruising</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
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<td></td>
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<tr>
<td></td>
<td>Constipation</td>
<td>13</td>
<td>0</td>
<td></td>
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<td>Vascular disorders</td>
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<td>12</td>
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</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>11</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalemia</td>
<td>14</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperemicis (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities (≥ 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Percent of Patients (N=118)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils decreased</td>
<td>45</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>40</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>27</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>41</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea increased</td>
<td></td>
<td>29</td>
<td>2.6</td>
</tr>
<tr>
<td>ALT increased</td>
<td></td>
<td>28</td>
<td>0.9</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td></td>
<td>24</td>
<td>8.9</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements.

† Amsyptomatic lymphocytosis is a known effect of BTK inhibition.
Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK ≥ 50 x 10⁹/L and an absolute neutrophil count ≥ 1 x 10⁹/L independent of growth factor support, hepatic Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory disorders Hypertension 12 3.4
Musculoskeletal and
Cough 12 0

Vascular disorders

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003. The most frequent adverse reaction leading to treatment discontinuation was any grade) (5%), hyperuricemia (6%) and headache (4.2%).

5.4 Second Primary Malignancies
Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 3-fold human exposures (see Data). Women should be advised to avoid pregnancy while taking BRUKINSA, if BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

5.6 Embryo-Fetal Toxicity

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily. Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

5.7 Hepatic Impairment

Rationale for the selection of the single-arm Phase 2 dose: The maximum tolerated dose of zanubrutinib in a Phase 1 study was 300 mg twice daily with a 12-hour interval between doses. Safety data in patients with atrial fibrillation were available in a single-arm Phase 2 study. The dose of 300 mg twice daily was selected for this study because it had been associated with a favorable safety profile in patients with atrial fibrillation and was well tolerated over 24 weeks of treatment. The recommended dose for patients with atrial fibrillation is 300 mg twice daily. The recommended dose for patients with mantle cell lymphoma is 300 mg twice daily. The recommended dose for patients with chronic lymphocytic leukemia is 160 mg twice daily.

5.8 Monitoring for Atrial Fibrillation

Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy.

5.9 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis (see Clinical Pharmacology (12.3)).

5.10 Pregnancy

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 3-fold human exposures (see Data). Women should be advised to avoid pregnancy while taking BRUKINSA, if BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

5.11 Lactation

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

5.12 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

5.13 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

6.1 Clinical Trials Experience

Table 5: Drug Interactions that Affect Zanubrutinib

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib Cmax and AUC [see Clinical Pharmacology (12.3)] which may increase the risk of BRUKINSA toxicity.</td>
<td>Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors [see Dosage and Administration (2.3)].</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women.

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Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 3-fold human exposures (see Data). Women should be advised to avoid pregnancy while taking BRUKINSA, if BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily. Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were ≥ 65 years of age, while 16% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment [see Drug Interactions (6.1)] if the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment [see Clinical Pharmacology (12.3)].

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Infrastructure of OCM Helps Practices Through COVID-19, Chong Says

MARY CAFFREY

“Nothing about taking care of patients with cancer during the coronavirus disease 2019 (COVID-19) pandemic has been easy, but those practices that had already embraced transformation under the Oncology Care Model (OCM) are finding that its monthly payments and other features offer stability during an unprecedented health emergency.

That’s what Alexandra Chong, PhD, lead for the OCM within the Center for Medicare and Medicaid Innovation (CMMI), told the hundreds of online attendees on September 25, 2020, as she kicked off the 9th annual meeting of Patient-Centered Oncology Care, the marquee annual event presented by The American Journal of Managed Care. “We are living in a totally different world,” said event Cochair Kashyap Patel, MD, who is CEO of Carolina Blood and Cancer Care Associates of Rock Hill, South Carolina, as he introduced Chong.

“What we are learning is how COVID-19 impacts not just as what we do in the office, but how it impacts the rapid adaptation and changes from the payer perspective.”

Chong spent much of her talk walking attendees through the fine points of the OCM, which had been poised to transition on January 1, 2021, to Oncology Care First (OCF), a next-generation model built on a bundled-payment framework instead of fee-for-service (FFS). As Chong explained, due to COVID-19, the OCM was extended another year through 2022, and CMMI has not yet fleshed out the details of OCF.

OCM is “an episode-based model,” Chong said, one that attaches 2 reimbursement elements to each practice’s commitment to reach certain financial and quality benchmarks while meeting practice standards that include having 24/7 access to medical records and developing care and survivorship plans with patient input. Although the number of practices in the OCM is 138, the number of physicians involved exceeds 7000, and the model now reaches 150,000 Medicare patients each year, or about a quarter of all FFS beneficiaries with cancer. Practices in the OCM receive $168 per patient per month in Monthly Enhanced Oncology Services (MEOS) for delivering this higher-level care, as well as Performance-based Payments which come after each 6-month evaluation period ends. As Chong explained, the work that practices undertook to redesign their procedures for the “high-touch” requirements of the OCM was not easy—and a learning process for both sides. But it’s paying dividends now. Practices that rely on administering expensive therapies—and having new patients walk through the door—have seen revenue plummet as people skip cancer screenings. But those in the OCM have had some lifelines.

“Participants have been able to not lose that momentum in providing high-quality care that they committed to their beneficiaries,” Chong said. By embracing the tools that make the OCM work, Chong said, “Participants have been able to not lose that momentum in providing high-quality care that they committed to their beneficiaries.”

To be sure, the OCM is not perfect, and Chong said CMMI has heard the message from participating physicians that it must rethink reporting requirements and turn around performance data in a time frame that lets practices fix problems quickly. Because of the epidemic, CMMI has made some data reporting requirements optional during the COVID-19 public health emergency, including aggregate quality measure reporting and beneficiary-level clinical and staging data reporting.

“A majority of our practices still reported on these data, even though doing so was optional,” Chong said.

Before COVID-19 hit, she noted, the OCM was gaining momentum as it headed into its final year. A third of the practices in the model had agreed to take on 2-sided risk or “some type of downside risk,” she said.

By embracing the tools that make the OCM work, Chong said, “We decided to retain the billing and to keep up those MEOS payments, because we have heard across…a majority of our practices, that a lot of the infrastructure that was put into place for the implementation of OCM has really helped our practices in terms of still achieving or [staying focused] on the the of their beneficiaries,” Chong said.

For these practices, the time and investment in “practice redesign activities” is paying off. These include (1) enhanced services, including offering patients or other providers 24/7 access to their medical records; (2) utilization data for quality improvement; and (3) providing a reconciliation on what performance looks like during the 6-month episodes in each performance period. Meeting the “high-touch” expectation means practices are connecting with patients more frequently than they might have under prior practice designs.

“A lot of the infrastructure that was put in place for the implementation of [the Oncology Care Model] has really helped our practices in terms of still achieving or [staying focused] on their beneficiaries” during COVID-19.

—Alexandra Chong, PhD, health insurance specialist and OCM lead, Center for Medicare and Medicaid Innovation

### TABLE 1. COVID-19 Flexibilities

<table>
<thead>
<tr>
<th>Innovation Center Model</th>
<th>Financial Methodology Changes</th>
<th>Quality Reporting Changes</th>
<th>Model Timeline Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology Care Model (OCM)</td>
<td>Option for OCM practices to elect to forgo upside and downside risk for performance periods affected by the PHE</td>
<td>Make the following optional for the affected performance periods:</td>
<td>Extend model for 1 year through June 2022</td>
</tr>
<tr>
<td></td>
<td>For OCM practices that remain in one- or two-sided risk for the performance periods affected by the PHE, remove COVID-19 episodes from the reconciliation for those performance periods</td>
<td>- Aggregate-level reporting of quality measures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Beneficiary-level reporting of clinical and staging data</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Remove the requirement for cost and resource utilization reporting and practice transformation plan reporting in July/August 2020</td>
<td></td>
</tr>
</tbody>
</table>
Implementation of Chronic Care Management and Telehealth in Oncology

ROSE MCNULTY

IN PRINCIPLE, THE CHRONIC CARE MANAGEMENT (CCM) services and billing codes introduced by the CMS in 2015 benefit physicians and patients. Physicians are reimbursed for extra care coordination services provided to patients with chronic conditions outside of office visits. Patients who otherwise may be more likely to visit the hospital can receive the monitoring they need to avoid being admitted. But like most ideas that are good in theory, it's a bit more complicated in practice.

Managing chronic conditions and the importance of telehealth and disparities in its use were the topics of discussion led by Patient-Centered Oncology Care® Cochair Kashyap Patel, MD, who is the CEO of Carolina Blood and Cancer Care Associates of Rock Hill, South Carolina. The panel included Roberta Buell, MBA, a nationally recognized expert in oncology reimbursement and principal for provider services and reimbursement information at onPoint Oncology Inc; Jhnnett Blakely, MD, executive director of health-related outcomes research at Tennessee Oncology; and Robert Daly, MD, MBA, a medical oncologist at Memorial Sloan Kettering Cancer Center.

A Practical Approach to CCM Billing

“I believe all oncologists do chronic care management,” Buell said at the start of the discussion. “You perform the task, but you don’t bill for it.”

Part of the confusion, she said, is that most are familiar with the original version of CCM, which required patients to have 2 or more chronic conditions expected to last 12 months or more, which put them at risk of unnecessary hospitalization or put their lives at risk. But there are now more billable services, including principal care management (PCM), which includes patients with just 1 chronic condition. Most of all, billing is not restricted to just 1 physician per month.

“When PCM came out last year, where you could focus on one problem and didn’t have to worry about whether other physicians were billing for it—all the restrictions that you were talking about with CCM—I thought it was going to sweep oncology,” Buell said. “And so far this year, I have zero [billings for it] in my database.”

Patel said a potential reason oncologists are not quick to adopt CCM is that the reimbursement may not seem significant enough. But that line of thinking can hurt a practice in a system that is change-fatigued field, it adds another box to tick.

Technology in Chronic Care Management: Benefits and Disparities

Telehealth has seen a boom in the coronavirus disease 2019 (COVID-19) pandemic, but there are serious disparities in availability. Patel said around 50% of the patients treated at his practice in rural South Carolina do not have access to Wi-Fi. With the potential benefits of telehealth care, this disparity needs to be addressed.

Daly cited a study presented at the plenary session of the American Society of Clinical Oncology’s meeting in 2017 that randomized patients to self-report symptoms between clinic visits. Those patients had a significant improvement in quality of life, fewer acute care visits and emergency department visits, and an improvement in overall survival, he said.

The next step, Daly said, is figuring out how to implement remote monitoring in clinical practices. That includes pinpointing the cadence at which remote check-ins should be done for optimal results and deciding which patients would most benefit.

Blakely said COVID-19 has taught providers a lot about telehealth and its effectiveness. Her practice partnered with an electronic platform to obtain data on its patients, which allowed physicians to identify when patients are most likely to visit the hospital and which patient groups are at a higher risk.

But there remains the question of how providers can implement telehealth when much of their patient population does not have access to technology that many take for granted. Daly cited investigator Kathi Mooney, PhD, RN, FAAN, of the University of Utah, who he said implemented a system in which patients could report symptom severity using a touch-style phone.

“As we’re noting that there’s potentially a survival advantage to this remote monitoring, we really don’t want to leave any patients out,” Daly said. “So, I think working with policy makers and working with patient advocates to make sure we can create solutions for all these patients is really important.”
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Managing the “Knowledge Explosion”
A Key Challenge of Precision Oncology

MARY CAFFREY

NEW THERAPIES. NEW TESTS. New technology to connect all the dots. Life for veteran medical oncologists looks almost nothing like it did at the start of their careers, which is both wonderful for patients and sometimes overwhelming to their physicians at the same time.

The panel on finding value in precision on oncology at Patient-Centered Oncology Care®, moderated by meeting Cochair Joseph Alvarnas, MD, took many turns as the physicians discussed sweeping changes that have converted many types of cancer to chronic conditions, along with the rise of genomic testing that allows them to more precise match therapy to a patient’s specific cancer.

But the panel featuring Edward R. Arrowsmith, MD, medical oncologist, Tennessee Oncology; David Debono, MD, medical director, oncology, Anthem; and Lee Schwartzberg, MD, chief medical officer, OneOncology, acknowledged that managing what Schwartzberg called the “knowledge explosion” takes new tools that didn’t exist decades ago, if one is to bring the right treatment to the right patient.

At the same time, the group said, oncologists are listening more to patient goals, which may be measured less in duration of survival time than in the quality of that time.

Anthem, Debono said, has responded with a pathways program, structured around patient-centered end points, as well as a 2-part oncology medical home that calls on practices to look at their process and to show improvement in quality. Keeping up with the constant change is difficult, he said. “There may very well be drugs and regimens that are FDA approved around (National Comprehensive Cancer Center) guidelines, but really don’t have those patient-centered end points such as quality of life or overall survival,” he said. “So, we really try to concentrate on what is the patient’s experience, and what are those end points?”

“When we really try to focus is what we hear each day from patients, and the things they’re interested in are overall survival and having a better quality of life,” Arrowsmith said. “That’s a real focus on toxicities of therapy. And that’s where I think precision oncology is so valuable.”

Schwartzberg agreed with Debono’s goals for the medical home. “We want to be patient centered; we want to employ care navigation. And in the context of this discussion today, we’re also interested in advancing precision oncology as a subset of person-centered medicine,” he said.

“It’s never been more exciting to be a practicing oncologist because of all the new tools we have at our disposal,” Schwartzberg said. Newer therapies can deliver better results with less toxicity, “exactly what we would want for everyone who has treatment for cancer.”

Both Alvarnas and Schwartzberg recalled past patients who had diseases such as chronic myeloid leukemia (CML) but were ill in the years before the existence of medicines that can now convert certain blood diseases to serious, but manageable, chronic conditions.

“Your really not just talking about incremental change,” Alvarnas said. “You’re talking about a fairly profound paradigm shift.”

“I remember the day imatinib came out and I switched all my patients,” Schwartzberg said. “Here it is 20 years later and 80% of them are still on imatinib. And I remember the 27-year-old with CML, who I treated a few years before [that day], who predictably at 4 years went into last crisis and died in a month. So, I think about that patient and she was just a few years too early for this.”

Two decades on, “we’re still understanding the power of targeting HER2, and it’s not a finished story,” Schwartzberg continued.

“We’re moving into the era of understanding pathways and the way cancer cells—which are extremely complex—work. Targeting [a single] particular driver alteration or checkpoint is not going to be the answer for most solid-tumor cancers, unfortunately.”

The expansion of comprehensive genomic profiling will help better understand what genes can be targeted, Schwartzberg said. But that’s just the start. Practitioners need a more comprehensive report from testing, not just on what drug should be given, but also what trials are available. “That’s the ecosystem,” he stated.

Alvarnas agreed, saying that Tennessee Oncology’s partnership with Sarah Cannon Research Institute means there is a constant focus on looking for clinical trial opportunities.

Alvarnas asked Debono how he believed payers respond in this “hyperdynamic” period of change. “It is difficult,” Debono acknowledged. “It’s a big challenge.” From a payer standpoint, he said, obstacles arise when drugs that are approved offer relatively small improvements in survival advantage. Some drugs can be too toxic, and it can hard to advise providers. Anthem’s pathways program features biomarkers to help address this, Debono said.

A Precision Medicine Approach
Schwartzberg said OneOncology began a molecular and precision medicine approach several years ago, “with the idea that we would recommend and by no means mandate” that patients with advanced cancers have comprehensive profiling as opposed to limited panels or single-gene assays.

This is because sometimes, later on in treatment, it’s hard to get a second biopsy. Sometimes, there’s not enough time. And there are “very good arguments” for comprehensive genomic profiling in lung cancer, an arena in which treatments proliferate, as well as in rectal cancer. In breast cancer, comprehensive testing has implications not just for the patient, but for families, Schwartzberg said. As liquid biopsies become more common, he predicted, the comprehensive profiling option will become less problematic.

But Debono, of Anthem, said the payer takes a “more cautious approach.” As data come in from the NCI-MATCH trial and the TAPUR study, biomarkers such as BRAF and microsatellite instability high seem promising, but another study Debono cited sequenced 2000 patients and offered recommendations to 700, but only 163 ended up getting targeted therapy, “and of those patients, only 23 had a partial response.”

Clearly, the oncology community is in broad agreement about some biomarkers, but as far as universal access to broad-panel genomic testing is concerned, “I think that’s a question that we haven’t quite answered,” Debono said.

Financial Toxicity
What about patients who cannot afford the “right” therapy? “This is literally the $64-million question,” Arrowsmith said. “And it’s one we really struggle with.”

Tennessee Oncology has an integrated pharmacy and helps patients seek foundation support, but it’s not easy: The practice works with Foundation Medicine to ensure support for patients who need help with access to testing.

He noted this is not an area that many physicians were trained to address. “I think this explosive increase in the price of drugs is something that we’re all going to have to deal with in the coming years,” predicts Arrowsmith.●
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**Addressing Cancer Disparities Requires Asking Questions, Putting Aside Assumptions**

**LAURA JOSZT**

**DESPITE PROGRESS IN CANCER TREATMENTS,** patients with cancer are still affected by disparities in care, incidence of disease, and outcomes.1 During a panel discussion at the Patient-Centered Oncology Care® 2020 conference, moderated by meeting Cochair Joseph Alvarnas, MD, vice president of government affairs, senior medical director for employer strategy, and clinical professor, City of Hope Comprehensive Cancer Center, and editor-in-chief, Evidence-Based Oncology®, speakers highlighted injustices in the US health care system, the risk of financial toxicity, and how providers can better ensure that patients achieve health equity.

Karen Winkfield, MD, PhD, executive director, Meharry-Vanderbilt Alliance, and Emeline Aviki, MD, MBA, assistant attending, Department of Surgery, Memorial Sloan Kettering Cancer Center, said they were first exposed to disparities as medical students at Duke University and then again when both started working in Boston. Medical students often went into rural or Black communities to try improving access to care, but Boston had universal health care coverage before passage of the Affordable Care Act. It was there that stark differences in access to care despite insurance coverage became apparent, Winkfield said.

"We are willing to pay tens of thousands of dollars a month for a 3-month progression-free survival difference. Well, we can gain that and more by addressing patients’ financial issues and social determinants, as well."

—Emeline Aviki, MD, MBA, assistant attending, Department of Surgery, Memorial Sloan Kettering Cancer Center

"It started me on this pathway to understand what some of the other barriers were," she said. "What are some of the issues that patients are experiencing with respect to their access to care, their inability, perhaps, to access care?"

Winkfield changed career paths from biochemistry to a focus on community engagement research, which she viewed as crucial to finding information that would “revolutionize” how health care engaged with communities.

Aviki had a slightly different path. During medical school, she also got her MBA, and through her research on alternative payment models and value-based care, she came to realize that the payment models focused on the finances for payers and providers but “left the patients out of the whole equation.” She began to do work on financial toxicity, a term describing the financial burden from direct and indirect health care costs on patients that can increase psychosocial distress and adversely affect patient outcomes and quality of life.

At MSKCC, Aviki serves on an affordability task force that attempts to improve awareness of patients who might be at risk of financial toxicity and to “educate providers and patients with respect to early signs of toxicity and how we can empower providers to attack that toxicity before it ever occurs.”

How do providers help enact change in the system? According to Jeanne Regnante, chief health equity and diversity officer, LUNGevity Foundation, health systems, providers, and other organizations need to start learning from one another and asking better questions.

“I think the work in this area requires humbleness, in general, and it requires somebody to always be aware that they might not know something and ask the question,” Regnante said.

Engaging with vulnerable communities means acknowledging that you don’t understand the challenges facing those individuals. LUNGevity recently went through its first phase of implicit bias training, during which the staff focused on assumptions.

Winkfield said humility is necessary in this area of work and in addressing and understanding how someone’s culture fits into their health and health care.

“I do not believe in cultural competency,” she said, indicating that this implies someone can watch a video and understand someone’s culture. “No, it’s really about humility.”

This humility applies to culture, finances, and even sexual identity. Instead of asking a woman about her husband, clinicians should ask more generally who lives at home with her.

“It’s the questions that you ask that can show people that you’re open to someone having a lifestyle that’s different from you, know the ‘mainstream,’” Winkfield said. She said medical schools have to do a better job of training people to ask questions.

One conversation that is difficult for providers to have involves cost of care. MSKCC surveyed its clinicians, and of 350 who responded, 95% said they want to help patients with financial issues during treatment. But the same proportion said they felt ill-equipped to ask the question because they didn’t know how to respond to the answer, Aviki said.

The taboo of asking financial questions needs to be eliminated, she said. Patients and doctors should feel comfortable with discussing financial issues. Aviki said making a habit of asking patients about such issues can help them feel more comfortable in raising the topic.

"We are willing to pay tens of thousands of dollars a month for a 3-month progression-free survival difference," she said. “Well, we can gain that and more by addressing patients’ financial issues and social determinants, as well.”

Ultimately, it will cost more money to establish the processes, hire employees and analyze data to address disparities, Regnante said. But spending that money will mean making more resources available and ensuring that innovations benefit all patients. Winkfield said the cost is up front, but the US health care system loses billions of dollars every year because of health disparities. Investing the money now will mean setting up patient navigation, doing financial toxicity screenings, and putting patients in touch with needed resources.

"Please take the time to get to know the person in front of you, and figure out what their needs are," Winkfield said. "We may not always be able to meet every single one of their needs, but just by asking, we will help to engender the trust that is vital to make sure our patients feel well cared for.”

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**REFERENCE**

**Indication and Usage**
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

**Select Safety Information**
Serious adverse events, including fatal events, have occurred with CALQUENCE, including serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, and atrial fibrillation and flutter. The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

Please see Brief Summary of full Prescribing Information on adjacent pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.

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Concomitant Use with Gastric Acid Reducing Agents
[see Drug Interactions (7) in the full Prescribing Information].

patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when

Clinical Trials Experience
As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of

Concomitant Use with Gastric Acid Reducing Agents
[see Drug Interactions (7) in the full Prescribing Information].

Recommended Dosage for Drug Interactions
Dose Modifications for Use with CYP3A Inhibitors or Inducers

Recommended Dose for Hepatic Impairment

Recommended Dose for Hepatic Impairment

CALQUENCE® (acalabrutinib) capsules, for oral use

INDICATIONS AND USAGE
For full Prescribing Information consult official package insert.

CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding)

Recommended Dose for Hepatic Impairment

Recommended Dose for Hepatic Impairment

Recommended Dose for Drug Interactions
Dose Modifications for Use with CYP3A Inhibitors or Inducers

Recommended Dose for Drug Interactions
Dose Modifications for Use with CYP3A Inhibitors or Inducers

Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers

Table 2: Recommended Dose Modifications

Table 3: Common Adverse Reactions (≥15% Any Grade) with CALQUENCE in Patients with CLL (ELEVATE-TN)

Recommended Dose for Hepatic Impairment

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Recommended Dose for Hepatic Impairment

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Dose Modifications for Use with CYP3A Inhibitors or Inducers
CALQUENCE® (acalabrutinib) capsules, for oral use

Other clinically relevant adverse reactions (all grades incidence ≥ 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy): included:

- Neoplasms: second primary malignancy (10%), non-melanoma skin cancer (5%)
- Cardiac disorders: atrial fibrillation or flutter (8%), hypertension (5%)
- Infections: herpesvirus infection (6%)

Table 6: Select Non-Hematologic Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CALQUENCE plus Obinutuzumab N=176</th>
<th>CALQUENCE Monotherapy N=179</th>
<th>Obinutuzumab plus CALQUENCE N=169</th>
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<tr>
<td>Urine acid increase</td>
<td>30 (17)</td>
<td>27 (16)</td>
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<tr>
<td>ALT increase</td>
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<td>AST increase</td>
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<td>29 (17)</td>
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<tr>
<td>Bilirubin increase</td>
<td>13 (7)</td>
<td>15 (8)</td>
<td>16 (9)</td>
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*Per NCI CTCAE version 4.03
† Includes electrolytes

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 3.9% and 2.8% of patients in the CALQUENCE combination arm and monotherapy arm, respectively.

ASCEND

The safety of CALQUENCE in patients with relapsed or refractory CLL was evaluated in a randomized, open-label study (ASCEND) (see Clinical Studies (14.2) in the full Prescribing Information). The trial enrolled patients with relapsed or refractory CLL, after at least one prior therapy and required hematopoietic transplants ≤ 2 times upper limit of normal (ULN), normal bilirubin ≤ 1.5 times ULN, and an estimated creatinine clearance ≥ 30 mL/min. The trial excluded patients having an absolute neutrophil count < 500 µL, platelet count < 100,000 µL, significant bone marrow dysfunction, or a requirement for strong CYP3A inhibitors or inducers. Patients randomized to CALQUENCE monotherapy included those with either varizen or equivalent vitamin K antagonists. In ASCEND, 154 patients received CALQUENCE (100 mg approximately every 12 hours until disease progression or unacceptable toxicity), 118 received idelalisib (150 mg approximately every 12 hours until disease progression or unacceptable toxicity) with up to 8 infusions of a rituximab product, and 30 received up to 6 cycles of bendamustine and a rituximab product. The median age was 68 years (range: 32-90); 67% were male; 92% were white; and 48% had an ECOG performance status of 0 or 1.

In the CALQUENCE arm, serious adverse reactions occurred in 29% of patients. Serious adverse reactions in > 5% of patients who received CALQUENCE included lower respiratory tract infection (6%). Fatal adverse reactions within 30 days of the last dose of CALQUENCE occurred in 2.6% of patients, including from second primary malignancies and infections.

In recipients of CALQUENCE, permanent discontinuation due to adverse reaction occurred in 10% of patients, most frequently due to second primary malignancies followed by infection. Adverse reactions led to dosing interruptions of CALQUENCE in 34% of patients, most often due to respiratory tract infections followed by neutropenia, and dose reduction in 3.9% of patients. Selected adverse reactions are described in Table 7 and non-hematologic laboratory abnormalities are described in Table 8. These tables reflect exposure to CALQUENCE with median duration of 15.7 months with 94% of patients on treatment for at least 6 months and 80% of patients on treatment for greater than 12 months. The median duration of exposure to idelalisib was 11.5 months with 72% of patients on treatment for greater than 6 months and 48% of patients on treatment for greater than 12 months. Eighty-three percent of patients completed 6 cycles of bendamustine and rituximab product.

Table 7: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND)

Table 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)

**Table 8: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worsening from Baseline in Patients Receiving CALQUENCE (ASCEND)**

**Laboratory Abnormality** | **CALQUENCE N=154** | **Combination with Rituximab Product N=118** | **Obinutuzumab plus CALQUENCE N=169** |
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<tr>
<td>All Grades (%)</td>
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*Per NCI CTCAE version 4.03
† Includes electrolytes

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day (G) 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 9-times the AUC in patients at the recommended dose of 100 mg approximately every 12 hours. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 2-3 times the AUC in patients at 100 mg approximately every 12 hours.

In a pre- and postnatal development study in rats, acalabrutinib was administered orally to pregnant animals during organogenesis, parturition, and lactation, at doses of 50, 100, and 150 mg/kg/day. Pneumonia (prolonged or difficult labor) and mortality of offspring were observed at doses ≥ 100 mg/kg/day. The AUC at 100 mg/kg/day in pregnant rats was approximately 2-3 times the AUC in patients at 100 mg approximately every 12 hours. Underdeveloped renal papillae was also observed in F1 generation offspring at 150 mg/kg/day with an AUC approximately 5-times the AUC in patients at 100 mg approximately every 12 hours.

**Lactation**

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

**Females and Males of Reproductive Potential**

**Pregnancy**

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.

**Contraception**

Females

CALQUENCE may cause embryo-fetal harm and dystocia when administered to pregnant women (see Use in Specific Populations (8.7) in the full Prescribing Information). Advise females of reproductive potential to use effective contraception during treatment with CALQUENCE and for at least 3 months following the last dose of CALQUENCE. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

**Pediatric Use**

The safety and efficacy of CALQUENCE in pediatric patients have not been established.

**Geriatric Use**

Of the 929 patients with CLL or MCL in clinical trials of CALQUENCE, 68% were 65 years of age or older, and 24% were 75 years of age or older. Among patients 65 years of age or older, 59% had Grade 3 or higher adverse reactions and 39% had serious adverse reactions. Among patients younger than age 65, 45% had Grade 3 or higher adverse reactions and 25% had serious adverse reactions. No clinically relevant differences in efficacy were observed between patients 65 years and younger.

**Hepatic Impairment**

Avoid administration of CALQUENCE in patients with severe hepatic impairment. The safety of CALQUENCE has not been evaluated in patients with moderate or severe hepatic impairment (see Recommended Dosage for Hepatic Impairment (2.2) and Clinical Pharmacology (12.3) in the full Prescribing Information).

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As Practices Await OCF Details, the Question of How to Factor in COVID-19 Emerges

MARY CAFFREY

AS 2020 BEGAN, the biggest challenge facing practices in the Oncology Care Model (OCM) was the transition—for some—to 2-sided risk. And that's still a challenge, but one compounded by a wild card that never factored into anyone's forecast:

What happens if a global pandemic keeps people from being screened for cancer, and from being diagnosed, and thus from being treated? What if treatment regimens must be redesigned to keep patients out of the office or the infusion center as much as possible?

It's not a good time to be thinking about moving even further down the payment reform road to Oncology Care First (OCF), and thus the successor to OCM has been delayed until 2022.

All the wild cards of 2020 were part of the discussion as Kashyap Patel, MD, cochair of Patient-Centered Oncology Care® 2020, led a panel discussion on shifting from the OCM to the OCF. Panelists were Aaron Lyss, MBA, director of Strategic Payer Relations, OneOncology; Terrill Jordan, LLM, JD, president and CEO, Regional Cancer Care Associates; Mariam Alboustani, RPh, clinical pharmacy manager, Pharmacy Services, Blue Cross Blue Shield of Michigan; and Randall A. Oyer, MD, medical director of oncology and the cancer institute at Lancaster General Health/Penn Medicine.

"The key word is collaboration. We all have to own a piece of taking better care of the member [and] of controlling the rising cost of health care, and I think that's the only way to succeed."

—Mariam Alboustani, RPh, clinical pharmacy manager, Pharmacy Services, Blue Cross Blue Shield of Michigan

Early in the day, Patel likened the OCM to "an architect's blueprint" of how cancer care should work, one that reflects the time and resources participants have invested to build it. He launched the panel discussion by asking what the OCF should look like when it's fully presented. Jordan said that the ground has shifted with coronavirus disease 2019 (COVID-19) and the Center for Medicare and Medicaid Innovation (CMMI) must acknowledge that the population who comes through the door post pandemic will be different. "We will have to think about that, and challenge CMS/CMMI to take that into account appropriately," he said.

CMMI had a brief stakeholders' meeting on November 4, 2020, to discuss its OCF outline, Patel said, but there has been little information since that time. Oyer said the concerns among practices remain: Physicians worry about improving outcomes, decreasing administrative burden, and maintaining revenue. "We are also concerned about what our patients are facing, making access available to people across our entire community, [and] providing quality outcomes and patient experience," Oyer continued. "And then we're all concerned about our organizations—we work in these organizations."

With financial stability at the practice level, Oyer said, it's hard to deliver good care and be a community resource. Doing things the right way depends on having resources to build a good team, he noted, adding, "One of the really good things that came out of OCM for us was that everybody on the team understood their value."

Like Jordan, Oyer values transparency. "People see a line of sight between what they do in their daily practice and what results they want to accomplish," he said.

Lyss said achieving buy-in throughout an organization was important for success in the OCM and will be even more so in the OCF. The challenges ahead only become achievable, he said, "through a culture throughout the organization that is committed to value and committed to evolve, adapting to change."

Practice transformation, said Lyss, "will take time. It's going to be really hard; there are no shortcuts."

Alboustani said her payer is working with practices on the data-sharing challenges of the OCM, but that success in shifting to value-based care isn't just about an individual model—it's about recognizing that value-based care isn't going away. "It's not a phase," she exclaimed. "It's probably going to become the norm down the line—and we all have to collaborate. We all have to work better into making this efficient for everyone—for the patient, for the plan, and for the provider."

As practice transformation evolves, Jordan said the concept of shared savings must do so as well. Practices cannot keep squeezing savings out of the practice of oncology—and it's a reason why some have left the OCM even as they embrace its transformation principles. "The idea that you're essentially judged against or measured against your own historic performance is, I think, a real problem," he said. "You should get measured against the market that you're in. The variability in those markets is significant."

Jordan said his practice started out in the COME HOME Project, a precursor to OCM. "You've already taken a lot of the actions that were necessary to reduce costs. And so your baseline is lower. It completely undercuts your efforts," he said. "In terms of where we're going, I think, we're probably headed toward capitation. That's what it looks like, in some form."

In the end, Alboustani said, "The lesson learned here is: What is the value we're providing for the member? [And] what is the value in cost containment for providers through plans?" she asked.

"The key word is collaboration. We all have to own a piece of taking better care of the member, [and] of controlling the rising cost of health care, and I think that's the only way to succeed."

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Pharmacy Times
The Effect of Biosimilars on Cancer Institutions During COVID-19
Read more at: https://bit.ly/3I2A05I
IN THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE (Pd)

ACHIEVE GREATER OUTCOMES FOR YOUR PATIENTS

SARCLISA is an anti-CD38 therapy proven to deliver superior PFS (median PFS of 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P<0.0010). SARCLISA also demonstrated a significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)*

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®)2

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.1
CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Indication
SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Important Safety Information
CONTRAINdications
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in 39% of patients treated with SARCLISA. All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an IRR included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea.

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally.

In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
**SARCLISA + Pd extended median PFS to ~1 year**

Superior PFS with SARCLISA + Pd vs Pd alone

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd. At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.

---

**SARCLISA + Pd showed a significant increase in ORR**

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(60.4%) ORR</td>
<td>(35.3%) ORR</td>
</tr>
<tr>
<td>(31.8%) (\geq) VGPR</td>
<td>(8.5%) (\geq) VGPR</td>
</tr>
<tr>
<td>35 days</td>
<td>58 days</td>
</tr>
</tbody>
</table>

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 66.2%), Pd (95% CI: 27.8%, 43.4%).

**STUDY DESIGN:** ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients \(\geq\) 75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint. ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.
Important Safety Information (cont’d)

Neutropenia
SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%). Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies
Second primary malignancies were reported in 3.9% of patients in the SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm), and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using diethytoxilol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were neutropenia (laboratory abnormality: 96% Isa-Pd vs 92% Pd), infusion-related reactions (38% Isa-Pd vs 0% Pd), pneumonia (31% Isa-Pd vs 23% Pd), upper respiratory tract infection (57% Isa-Pd vs 42% Pd), and diarrhea (26% with Isa-Pd vs 19% Pd). Serious adverse reactions occurred in 62% of patients receiving SARCLISA. Serious adverse reactions in ≥5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

USE IN SPECIAL POPULATIONS
Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see accompanying brief summary of full Prescribing Information.


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SARCLISA™ Rx Only (isatuximab-irfc) injection, for intravenous use

1 INDICATIONS AND USAGE

SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. 

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

• Administer pre-infusion medications [see Dosage and Administration (2.2.1)].
• SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and personnel capable of providing medical support for management of infusion-related reactions if they occur [see Warnings and Precautions (5.1)].

The recommended dose of SARCLISA is 10 mg/kg actual body weight (as a 150 mL infusion volume containing 0.9% sodium chloride USP or dextrose 5% in water USP) or 0.22 mg/kg intravenous injection volume (as a 150 mL infusion volume containing 0.9% sodium chloride USP or dextrose 5% in water USP) at room temperature. 

Dose reduction of SARCLISA may be required to allow recovery of blood counts in the event of infusion-related reactions if they occur [see Warnings and Precautions (5.1)].

2.2 Recommended Premedications

Administer the recommended premedication agents 15 to 60 minutes prior to the recommended premedication is given to patients to be administered only once before infusion as part of the pretreatment and of the background treatment, before SARCLISA and pomalidomide administration. 

Admister the recommended premedication agents 15 to 60 minutes prior to starting a SARCLISA infusion.

2.3 Dosing Schedule

No dose reduction of SARCLISA is recommended. Dose delays may be required to allow recovery of blood counts in the event of hematological toxicity [see Warnings and Precautions (5.2.4)]. For information on dosing given in combination with SARCLISA, see manufacturer's prescribing information. 

For other medicinal products that are administered with SARCLISA, refer to the respective current prescribing information.

2.4 Preparation

Prepare the solution for infusion using aseptic technique as follows: Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each course to have the administered dose adjusted accordingly) [see Dosage and Administration (2.1)]. More than one SARCLISA vial may be necessary to obtain the required dose for the patient.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Remove the volume of dilt from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP dilt bag that is equal to the required volume of SARCLISA injection.

Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to achieve the appropriate SARCLISA concentration for infusion.

The infusion bag must be made of polyolefin (PD), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).

Gently homogenize the diluted solution by inverting the bag. Do not shake.

2.5 Administration

Administer the reconstituted solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutyleneterephthalate [PBT], or polyethylene [PU]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).

The infusion solution should be administered for a period of time sufficient to complete the infusion (see Table 2). Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C–8°C, followed by 8 hours (including the infusion time) at room temperature.

Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.

Infusion Rates

Following administration, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only if there is no infusion-related reaction [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

Table 2: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Days 1, 8, 15 and 22 (weekly)</td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
</tr>
</tbody>
</table>

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

SARCLISA is administered in combination with pomalidomide and dexamethasone.

Missed SARCLISA Doses

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.5 Recommended Premedications

SARCLISA is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min), history of hypersensitivity to isatuximab-irfc or to any of its excipients [see Warnings and Precautions (5.1)].

2.6 Infusion-Related Reactions

Infusion-related reactions have been observed in 9% of patients treated with SARCLISA [see Adverse Reactions (6.1)]. All infusion-related reactions occurred during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an infusion-related reaction were chills, nausea, and headache. The most common severe signs and symptoms included hypotension and dyspnea [see Adverse Reactions (6.1)]. To decrease the risk and severity of infusion-related reactions, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent; dexamethasone [see Dosage and Administration (2.2.1)]. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 [see Dosage and Administration (2.2.1)]. In case symptoms do not improve after restarting, permanently discontinue SARCLISA therapy if a grade 3 or higher infusion-related reaction occurs and institute appropriate medical management.

5.2 Neutropenia

SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 98% of patients and grade 3-4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone ( Isa-Pd) (n=149) [see Clinical Studies (14)]. The incidence of grade 4 neutropenia delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10⁹/L and provide supportive care with growth factors as recommended [see Warnings and Precautions (5.2)]. No dose reductions of SARCLISA are recommended.

5.3 Second Primary Malignancies

Second primary malignancies were reported in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2 patients in the Isa-Pd arm) and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm) and myelodysplastic syndrome (0.7% of patients in the Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies [see Clinical Studies (14)], International Myeloma Working Group (IMWG) guidelines.

5.4 Laboratory Test Interference

Interference with Serum Protein Electrophoresis and Immunofixation

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein [see Drug Interactions (7.1)].

5.5 Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to pregnant women. SARCLISA may cause fetal cell immune depletion and decreased bone density. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to avoid an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose [see Use in Specific Populations (8.1, 8.3)]. The combination of SARCLISA with pomalidomide and dexamethasone may increase the risk of severe poikilocrposite bone disease in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information for further information regarding pregnancy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling: SARCLISA infusion-related reactions [see Warnings and Precautions (5.1)], Neutropenia [see Warnings and Precautions (5.2)], Secondary Malignancies [see Warnings and Precautions (5.3)].

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 in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Multicenter Experience

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial. The clinical trials of SARCLISA were conducted in 1,412 patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/µL, absolute neutrophil count ≥1.0 x 10⁹/L, creatinine clearance ≥30 mL/min (MDRD formula), and AST and ALT ≤1.5 x ULN. Patients received SARCLISA 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and low dose dexamethasone (Pd) (n=152) or pomalidomide and low dose dexamethasone (Pd) (n=149) [see Clinical Studies (14)] in the full prescribing information. Among patients receiving Isa-Pd, 66% were exposed to SARCLISA for 6 months or longer and 24% were exposed for greater than 12 months or longer. The median age of patients who received Isa-Pd was 68 years range: 36–83), 56% male, 76% white, and 14% Asian. Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in 5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients that occurred in more than 1% of patients. Serious adverse reactions include pneumonitis and other infections (3%).

Permanent discontinuation due to an adverse reaction grade 3–4 occurred in 7% of patients receiving Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (5%). In addition, Isa-Pd was permanently discontinued in 3% of patients due to infusion-related reactions. Dosage interruptions due to an adverse reaction occurred in 3% of patients receiving Isa-Pd. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).
The most common adverse reactions (≥20%) were neutropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea. Table 3 summarizes the adverse reactions in ICARIA-MM.

Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Ia-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reactions</td>
<td>38 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infections</td>
<td>32 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>21 (14%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Spleen palpable</td>
<td>12 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>12 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Blood and lymphatic system disorders**

- Absolute neutrophil count below 1000/mm³: 12 (8%) vs. 0 (0%)
- Eosinophilia: 12 (8%) vs. 0 (0%)
- Neutropenia: 11 (7%) vs. 1 (1%)
- Thrombocytopenia: 9 (6%) vs. 1 (1%)

**Hematologic laboratory abnormalities**

Table 4 summarizes the hematology laboratory abnormalities in ICARIA-MM.

Table 4: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment — ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Ia-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
<th>P= Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>48 (32%)</td>
<td>0 (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>46 (31%)</td>
<td>0 (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>46 (31%)</td>
<td>0 (0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22 (15%)</td>
<td>2 (1%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Description of Selected Adverse Reactions**

**Infusion-related reactions**

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 20-24 hours from the start of the infusion) were reported in 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) having infusion-related reactions at their 2nd infusion and 2 patients (1%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 3.2%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypotension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to infusion interruption was 55 minutes.

In a separate study (TQD 14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 40% of the patients after the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

In ICARIA-MM, the incidence of Grade 3 or higher infections was 45% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 13.2% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 0.7% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.

6.2 Immunogenicity

As with all monoclonal antibodies, there is a potential for immunogenicity. 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 population, sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other bispecific mAb products may be misleading.

In ICARIA-MM, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single agent and combination therapies including ICARIA-MM (N=546), the incidence of treatment emergent ADA was 2.3%. No clinically significant differences in the pharmacoekinetics, safety, or efficacy of isatuximab-irf was observed in patients with ADAs.

7 DRUG INTERACTIONS

7.1 Laboratory Test Interference

Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serological tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA [see Warnings and Precautions (5.4)]. Interference with Serum Protein Electrophoresis and Immunofixation Testing

SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-proteins. Interference with accurate response classification based on International Myeloma Working Group (IMWG) criteria [see Warnings and Precautions (5.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irf-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models [see Data]. The effects of SARCLISA use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicology studies have not been conducted with isatuximab-irf. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy. Pomalidomide is only available through a REMS program.

Clinical Considerations

Fetal/neonatal reactions

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Refer to the pomalidomide prescribing information for use in neonates and infants administered to the mother.

8.2 Lactation

Risk Summary

There are no available data on the presence of isatuximab-irf in human milk, milk production, or the effects on the breastfed child.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Pomalidomide can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to starting treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 53% (306 patients) were 65 or over, while 14% (62 patients) were 75 or over. There was no overall difference in safety or effectiveness between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years and over and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

There is no known specific antidote for SARCLISA overdose. In the event of overdose of SARCLISA, monitor the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.

Manufactured by:

Sanofi-Aventis U.S. LLC
Bridgewater, NJ 08807
Sanofi Company
U.S. License No. 1752

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ISA-BPLR-SA-MAR20

Revised: March 2020

Data

Animal data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).
How Education, Access Can Optimize Value-Based Cancer Care Delivery

MATTHEW GAVIDIA

AS HE OPENED HIS TALK during this year’s Patient-Centered Oncology Care® 2020 conference, Harlan Levine, MD, president of strategy and business ventures at the City of Hope comprehensive cancer center, highlighted the chasm present in oncology today.

“One hand, it’s an amazing time in oncology with great discoveries that could help people. On the other hand, the system itself is struggling with both affordability and access,” he said.

Levine said getting the most from innovation within oncology care requires the US health care industry to reimagine how cancer care is delivered. He said it calls for understanding how cancer is different from all other clinical conditions, particularly when considering strategies best suited for other diseases.

In examining models tailored to manage diabetes or cardiovascular disease, for instance, Levine said the pathways have clear, established goals, specific interventions backed by evidence, and measures that tend to align with patient interest. He compared these dynamics with cancer care, which affects approximately 0.5% of the general population in new diagnoses each year, and said best practices in oncology are rapidly evolving.

Building on the differences between cancer and other clinical diseases, Levine said that in oncology, typically the first chance of cure is the best. The timeframe afforded to physicians managing patients with diabetes or high cholesterol differs from that for patients with cancer, with patient behaviors (exercise, smoking cessation) also not having extensive effect on care in oncology.

Although patient participation is important, medical interventions of chemotherapy, radiation, and surgery make the biggest difference in oncology. Levine said.

Cost also presents a significant obstacle for those seeking cancer care, with many of the latest innovations in treatment totaling hundreds of thousands, if not millions, of dollars. Delving into the current landscape of value-based health care in oncology, Levine said that among payers, process measures are still prioritized instead of variables such as survival and quality of life.

To address the challenges of value-based care in oncology, Levine said defining value is the first step. It must capture how patients weigh the value of their care.

“So let’s take a look at how the current tools work in oncology specifically, and then if we decide they aren’t applicable, let’s be willing to let go of old habits and not do just what is easy for us to do,” Levine said. “Let’s try to start with a new design, a new vision where we make the cancer patient and their family the primary customer, and then when you do that, then you’re at a point where you can really begin to build a new model for the future.”

The setting in which patients with cancer receive care can play a significant role, Levine said, with a 20% difference in 5-year survival observed among patients in a National Cancer Institute-designated cancer center compared with those attending community practice and acute medical centers.

Although he did not suggest that every patient should be treated in these centers, Levine said a significant catalyst for this survival difference is use of genomics, which he said has revolutionized how physicians think about, treat, and diagnose cancer. A major issue is the pace at which cancer care is evolving; it can become daunting for oncologists, with 4 out of 5 having said in multiple surveys that they are not completely confident in their ability to keep up with the changes.

“This is not a negative comment about community oncologists. In fact, they play a key role, but it’s just a comment to say the world is different,” Levine said. “Genomics is changing everything, and we need to do something to fill that gap.”

This deficit in equitable cancer care poses a challenge, especially among those who do not live near major cancer centers. Levine said the primary goal should not be to create a system where every patient with cancer goes to a major center, but rather to find ways to help community oncologists receive the latest expertise to ensure that variables crucial to value-based cancer care, such as survival and quality of life, are prioritized. Additionally, eliminating low-value care can prove significant in terms of cost and quality for oncology practices.

When assessing tools available today in oncology, including narrow networks, accountable care organizations, and centers of excellence, each option has the potential to improve care delivery, but all are evolving and subject to issues related to cost and availability.

These factors are what Levine and his colleagues at City of Hope account for when strategizing how to optimally create a system that delivers the care that patients and their respective family members want without subjecting them to high cost.

“We need to acknowledge that both academic medicine and community medicine have value, and we need to find a balance between the two,” he said. “For complex cancers or for those with rapid-changing best practices, we need to get access to expertise. We need to focus incentive payments on delivering the best care, not necessarily the lowest-cost drug,” Levine said.

Continuing the discussion on steps needed to improve cancer care, Levine spoke on myriad issues, including the implementation of decision support programs, assisting patients in finding clinical trials, and improving access and outcomes for certain minority, racial, and ethnic groups. Levine highlighted the creation of a separate entity within City of Hope, called Access Hope, that works to educate cancer centers nationwide about the latest innovations in oncology and reconfigure how value-based interventions could occur.

Levine cited the need for efficiency in oncology, not only to improve treatment and outcomes, but to reduce costs as well. Ensuring community cancer centers have the expertise and tools necessary to provide uniform care nationwide can also assist in bridging the gap present in oncology, he said.

“Really, what’s important is we’re able to do it in the convenience of one’s market. So the patient, the family don’t feel like they’ve had their lives disrupted to get value-based care, while at the same time, having access to all the great changes that are happening in the oncology revolution today,” Levine said.

REFERENCE
Many Biosimilars Coming, but Objectives Not Always Aligned

TONY HAGEN

A FLOOD OF BIOSIMILARS can be anticipated during the next 5 years, which will reshape the current biosimilar landscape of 28 approved and 17 marketed products, with a consequent shifting of the sands for originator drug products and their dominance, predicted Sean McGowan, MBA, senior director of biosimilars for AmerisourceBergen, a drug wholesaler.

However, McGowan and other panelists in a discussion at The American Journal of Managed CARE®’s Patient-Centered Oncology Care® 2020 virtual conference agreed that there’s plenty of disconnect when it comes to harmonizing the objectives of stakeholders to ensure biosimilar access at lowest cost.

The biosimilar revolution is gathering speed and mass, and many of its systemic problems have to do with the growing competitiveness of the market and the inability to engineer solutions quickly enough, McGowan said.

“I’m very optimistic about the biosimilar product category and its ability to deliver the same level of efficacy and safety [as innovator products] from a clinical perspective, but then also to drive significant cost savings for providers, patients, and the health system as a whole,” he said.

Bhavesh Shah, RPh, BCOP, senior director of specialty and hematology-oncology pharmacy services at Boston Medical Center Health System, agreed with McGowan that solutions to these problems are in development. “Biosimilars are actually pretty important in the minds of many institutions because these are the low-hanging fruit that are going to bring a lot of savings to institutions immediately,” he said. At Boston Medical, an estimated 90% of patients in oncology now have biosimilars available as treatments, he said.

Coronavirus disease 2019 (COVID-19) has stressed finances, causing major losses for the health care system and a painful hit to the wallet for patients, but these factors may stimulate biosimilar uptake, panelists said. “I do think COVID-19 is actually going to bring up more aggressive biosimilar adoption because of the financials we’re seeing,” McGowan said.

Kashyap Patel, MD, panel moderator and event cochair, said the evidence backing that statement is seen in the patients who have lost jobs and insurance coverage and not been able to continue with routine care or access screening because of distancing precautions. Cancer progression is one consequence of this interruption in care. “I do see that getting worse over the next 3 to 4 months as we enter the second wave of [COVID-19],” he said.

Patel is CEO of Carolina Blood and Cancer Care Associates in Rock Hill, South Carolina, and said that 6 months from now he expects biosimilars to have shaved 20% from his total drug spending, based on the discounts already available by using them. But operations would be less complicated if payer policies on biosimilars were better aligned with practice realities, he said. CMS will cover any approved biosimilar, but the same is not true among private payers, which tend to narrow the range of biosimilars available to providers based on the sourcing deals they have been able to obtain.

Speaking for the payer side of the argument was Karina Abdallah, PharmD, a strategist and outcomes expert with Blue Cross Blue Shield of Michigan. COVID-19 has been a distraction in terms of working to improve biosimilar access, she said, adding that formulary decisions must be based on business realities as well as clinical needs. “Most of our decisions have been based on, at the minimum, the inclusion of 1 biosimilar or 2 biosimilar options to kind of open up that market, but we take rebates into consideration, of course, because that does include getting it down to how much we are paying per claim, which then ultimately comes back to how we handle all of our premiums and also [all] of our savings to make it affordable for patients.”

Payer decisions to restrict biosimilar access to a small number of available products creates a problem for practices, Patel said. “If I have to keep 20 vials of each different biosimilar, it becomes difficult for us to manage,” he said, raising the question of why payers and providers can’t work together to resolve these problems.

McGowan said payer restrictions on biosimilars are an almost universal complaint among health care centers that administer these products to patients. “I don’t think anybody was really talking about this when there were very few biosimilars in the market for several years. We really didn’t see competitive markets emerge until late 2018, early 2019, down into 2020. So, it’s kind of a double-edged sword, where there is choice, there is access, but then at the same time it’s on the clinicians and those who are directing pharmacy activities to have to manage carrying multiple biosimilars for the same indications.”

That said, widespread concern and discussion on this topic have led to some creative solutions, “where practices and health systems are getting more savvy and leveraging their technology, their IT infrastructure, their [electronic medical records], to kind of alleviate and address these issues,” McGowan said. “I think it’s just the complexity of the market and how fast the market is evolving, and how much more competitive each of these markets is becoming, and how quickly some of these products are coming to market. The speed of the evolution is happening a lot faster than I think the solutions can kind of address or alleviate them.”

Shah said stakeholders need to be educated about the dynamics of the situation. “You know, providers are so busy trying to remember which trastuzumab they ordered for which patients last. It’s just not optimal. Then what happens is that we’ll get more denials, and it’s now impacting the provider negatively financially when we’re trying to promote cost savings. “But if we get ahead of it and talk to the payers, I think that really would be helpful,” he said. Further, Shah said, there have been legislative actions taken. “What I’ve seen recently come about is certain states are putting together regulations or already have regulations that prevent payers from preferring one biosimilar over another and prevent a payer from preferring a reference product over a biosimilar. California is one of those states. There definitely are changes going on across the country, because we’re seeing this gaming of the system that’s happening for rebates, and it’s definitely not good for biosimilar adoption.”

Abdallah said Blue Cross Blue Shield is open to those discussions, but she defended the payer’s actions on biosimilars and said it, too, is working to create a market for these lower-cost drugs. “We were actually one of the first to really disrupt the market and go with a biosimilar-first approach. A lot of times we do forgos a very hefty rebate the originator product [company] is offering because we are looking to have adoption of biosimilars. I think that collaboration [with all stakeholders] is definitely something that a lot of payers are open to.”
Non–Hodgkin’s Lymphoma (NHL)
TRUXIMA is indicated for the treatment of adult patients with:

INDICATIONS
CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens

LEUKOENCEPHALOPATHY
Adverse reactions can occur in patients receiving rituximab products TRUXIMA, can result in serious, including fatal, infusion-related reactions.

HBV reactivation
Reactions and provide medical treatment for Grade 3 or 4 infusion-related infusion. Monitor patients closely. Discontinue TRUXIMA infusion for severe toxic epidermal necrolysis. The onset of these reactions has been variable and may occur during and following the completion of rituximab product-based therapy.

Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and life-threatening pancytopenia may occur, leading to death.

Cardiovascular Adverse Reactions
Infusion-related reactions have occurred more frequently in patients with myocardial infarction, cardiac arrest, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Cardiac arrhythmias may also occur in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy.

Infections
Infections have been reported in patients with prolonged neutropenia, severe, active infections, and high tumor burden, conferring the risk of severe, life-threatening infections. Patients with severe, progressive infections, such as sepsis, should receive appropriate antimicrobial therapy and continue anti-CD20 therapy. In severe cases, increase in bilirubin levels, liver failure, and death can occur in patients treated with drugs classified as PML inhibitors.

Embryo-Fetal Toxicity
Use of concomitant immunosuppressants other than corticosteroids has not been studied in combination with TRUXIMA. Use of concomitant immunosuppressants other than corticosteroids has not been studied in combination with TRUXIMA. Based on human data, rituximab products can cause fetal harm due to B-cell depletion and the absence of mature T cells and can occur in patients receiving rituximab products.

Use in RA Patients Who Have Not Had Prior Inadequate Response to TNF Antagonists
Based on human data, rituximab products can cause fetal harm due to B-cell depletion and the absence of mature T cells and can occur in patients receiving rituximab products.

PML Infection
Infections have been reported in some patients with prolonged neutropenia, severe, active infections, and high tumor burden, conferring the risk of severe, life-threatening infections. Patients with severe, progressive infections, such as sepsis, should receive appropriate antimicrobial therapy and continue anti-CD20 therapy. In severe cases, increase in bilirubin levels, liver failure, and death can occur in patients treated with drugs classified as PML inhibitors.

Severe Mucocutaneous Reactions
Severe mucocutaneous reactions can occur in patients receiving rituximab products. Severe mucocutaneous reactions can occur in patients receiving rituximab products. Severe mucocutaneous reactions can occur in patients receiving rituximab products.

Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with rituximab products, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with TRUXIMA. Discontinue TRUXIMA and concomitant medications in the event of HBV reactivation.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab products.

Important Safety Information
Boxed Warnings
Warning: Fatal infusion-related reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy

Infusion-related reactions (IRR) can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes. Rituximab product-induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, dyspnea, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with antihistamine and acetaminophen prior to dosing. For RA, GPA, and MPA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue TRUXIMA. Resume infusion at a maximum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm^3).

Severe Mucocutaneous Reactions
Severe mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab products. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. Discontinue TRUXIMA in patients who experience these reactions. The safety of re-administration of rituximab products to patients with severe mucocutaneous reactions has not been determined.

Initial approval in the US, November 2018.

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THE FIRST FDA-APPROVED BIOSIMILAR RITUXIMAB®
IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hepatitis B Virus Reactivation

• Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab products. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

• HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

• Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TRUXIMA. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TRUXIMA treatment.

• Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following completion of rituximab therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

• In patients who develop reactivation of HBV while on TRUXIMA, immediately discontinue TRUXIMA and any concomitant chemotherapeutic and immunostimulatory treatment. Insufficient data exist regarding the safety of resuming TRUXIMA treatment in patients who develop HBV reactivation. Resumption of TRUXIMA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Progressive Multifocal Leuкоencephalopathy (PML)

• JC virus infection resulting in PML and death can occur in rituximab product-treated patients with hematologic malignancies. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

• Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

• Discontinue TRUXIMA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Tumor Lysis Syndrome (TLS)

• Acute renal failure, hyperkalemia, hypercalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12–24 hours after the first infusion of rituximab products in patients with NHL. A high number of circulating malignant cells (>25,000/mm³) or high tumor burden, confers a greater risk of TLS.

• Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including diacid as indicated.

Infections

• Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab product-based therapy. Infections have been reported in some patients with prolonged hyogammaglobulinemia defined as hyogammaglobulinemia (>11 months after rituximab exposure) with or reactivated viral infections including cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue TRUXIMA for serious infections and institute appropriate anti-infective therapy. TRUXIMA is not recommended for use in patients with severe, active infections.

Cardiovascular Adverse Reactions

• Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving rituximab products. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of TRUXIMA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal Toxicity

• Severe, including fatal, renal toxicity can occur after rituximab product administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and TRUXIMA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue TRUXIMA in patients with a rising serum creatinine or oliguria.

Bowel Obstruction and Perforation

• Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation or perforation was 6 (range 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

Immunization

• The safety of immunization with live viral vaccines following rituximab product therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.

• Prior to initiating TRUXIMA physicians should ensure patients’ vaccinations and immunizations are up-to-date with guidelines. Administration of any non-live vaccines should occur at least 4 weeks prior to a course of TRUXIMA.

Embryo-Fetal Toxicity

• Based on human data, rituximab products can cause fetal harm due to B-cell lymphopenia in infants exposed to rituximab in utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving TRUXIMA and for 12 months following the last dose of TRUXIMA.

Concomitant Use With Other Biologic Agents and DMARDS Other Than Methotrexate

• Observation patients closely for signs of infection if biologic agents and/or DMARDS are used concomitantly as limited safety data is available.

• Use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA patients exhibiting peripheral B-cell depletion following treatment with rituximab products.

Use in RA Patients Who Have Not Had Prior Inadequate Response to TNF Antagonists

TRUXIMA should only be used in patients who have had a prior inadequate response to one or more TNF antagonist.

Most common adverse reactions in clinical trials of NHL (≥25%): infusion-related reactions, fever, lymphopenia, chills, infection, and arthritis.

Most common adverse reactions in clinical trials of CLL (≥25%): infusion-related reactions and neutropenia.

Most common adverse reactions in clinical trials of RA (≥10%): upper respiratory tract infection, nasopharyngitis, urininary tract infection, and bronchitis (other important adverse reactions include infusion-related reactions, serious infections, and cardiovascular events).

Most common adverse reactions in clinical trials of GPA and MPA (≥15%): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, and infusion-related reactions.

Nursing Mothers

There are no data on the presence of rituximab in human milk, the effect on the breastfed child, or the effect on milk production. Since many drugs including antibodies are present in human milk, advise a lactating woman not to breastfeed during treatment and for at least 6 months after the last dose of TRUXIMA due to the potential for serious adverse reactions in breastfed infants.

Please see the Brief Summary of Prescribing Information, including BOXED WARNINGS on the following pages.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

Initial U.S. Approval: 2018

TRUXIMA (rituximab-abbs) is biosimilar* to RITUXAN® (rituximab)

WARNING: FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion-Related Reactions

Administration of rituximab products, including TRUXIMA, can result in serious, including fatal, infusion-related reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion-related reactions occurred in association with the first infusion. Monitor patients closely. Discontinue TRUXIMA infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions [see Warnings and Precautions (5.1), Adverse Reactions (6.1)].

Severe Mucocutaneous Reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab products. See Warnings and Precautions (5.2).

Hepatitis B Virus (HBV) Reactivation

HBV reactivation can occur in patients treated with rituximab products, in some cases resulting in fulminant hepatitis, hepatitis failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients treated and after treatment with TRUXIMA. Discontinue TRUXIMA and concomitant medications in the event of HBV reactivation [see Warnings and Precautions (5.3)].

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab products [see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].

1 INDICATIONS AND USAGE

1.1 Non-Hodgkin's Lymphoma (NHL)

TRUXIMA (rituximab-abbs) is indicated for the treatment of adult patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with a line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressive (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.2 Chronic Lymphocytic Leukemia (CLL)

TRUXIMA is indicated, in combination with fludarabine and cyclophosphamide (FL), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)

TRUXIMA, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

1.4 Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

TRUXIMA, in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

2 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Rituximab products can cause severe, including fatal infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab product-induced infusion-related reactions include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA, GPA and MPA patients, methyprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue TRUXIMA. Resume infusion at a minimum 50% reduction in rate when infusion-related reactions have resolved. Closely monitor the following patients with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (>25,000/mm³) [see Warnings and Precautions (5.7), Adverse Reactions (6.1)].

5.2 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab products. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure.

Discontinue TRUXIMA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of rituximab products to patients with severe mucocutaneous reactions has not been determined.

5.3 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytotoxic antibodies. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBc] positive).

HBV reactivation is defined as an abrupt increase in alanine transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur. Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TRUXIMA. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TRUXIMA treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following TRUXIMA therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

In patients who develop reactivation of HBV while on TRUXIMA, immediately discontinue TRUXIMA and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TRUXIMA treatment in patients who develop HBV reactivation. Resumption of TRUXIMA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in rituximab product-treated patients with hematologic malignancies or with autoimmune disorders. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Patients with autoimmune disorders have prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Discontinue TRUXIMA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.5 Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12–24 hours after the first infusion of rituximab products in patients with NHL. A high number of circulating malignant cells (>25,000/mm³) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities and fluid balance, and administer supportive care, including dialysis as indicated [see Warnings and Precautions (5.8)].

5.6 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab product-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue TRUXIMA for serious infections and institute appropriate anti-infective therapy [see Adverse Reactions (6.1)]. TRUXIMA is not recommended for use in patients with severe, active infections.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

5.7 Cardiovascular Adverse Reactions
Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving rituximab products. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of TRUXIMA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina [see Adverse Reactions (6.1)].

5.8 Renal Toxicity
Severe, including fatal, renal toxicity can occur after rituximab product administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and TRUXIMA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue TRUXIMA in patients with a rising serum creatinine or oliguria [see Warnings and Precautions (4.5)].

5.9 Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab products in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.10 Immunization
The safety of immunization with live viral vaccines following rituximab product therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment. For patients treated with TRUXIMA, physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating TRUXIMA and administer live vaccines at least 4 weeks prior to a course of TRUXIMA.

The effect of rituximab on immune responses was assessed in a randomized, controlled study in patients with RA treated with rituximab and methotrexate (MTX) compared to patients treated with MTX alone. A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with rituximab plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the rituximab plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%). A positive response to tetanus toxoid vaccine (a T-cell dependent antigen) with existing immunity was similar in patients treated with rituximab plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on rituximab plus MTX vs. 70% of patients on MTX alone).

Most patients in the rituximab-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

5.11 Embryo-Fetal Toxicity
Based on human data, rituximab products can cause fetal harm due to B-cell lymphocytopenia in infants exposed in utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving TRUXIMA and for at least 12 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVRECTIONS
The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion-related reactions [see Warnings and Precautions (5.1)].
- Severe mucocutaneous reactions [see Warnings and Precautions (5.2)].
- Hepatitis B reactivation with fulminant hepatitis [see Warnings and Precautions (5.3)].
- Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.4)].
- Tumor lysis syndrome [see Warnings and Precautions (5.5)].
- Infections [see Warnings and Precautions (5.6)].
- Cardiovascular adverse reactions [see Warnings and Precautions (5.7)].
- Renal toxicity [see Warnings and Precautions (5.8)].
- Bowel obstruction and perforation [see Warnings and Precautions (5.9)].

6.1 Clinical Trials Experience in Lymphoid Malignancies
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 clinical practice.

The data described below reflect exposure to rituximab in 2783 patients, with exposures ranging from a single infusion up to 2 years. Rituximab was studied in both single-arm and controlled trials (n=356 and n=2427). The population included 1180 patients with low grade or follicular lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received rituximab as an infusion of 375 mg/m² per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received rituximab 357 mg/m² as an initial infusion followed by 500 mg/m² for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of rituximab-based therapy.

The most common adverse reactions of rituximab (incidence ≥25%) observed in clinical trials of patients with NHL were infusion-related reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of rituximab (incidence ≥25%) observed in clinical trials of patients with CLL were: infusion-related reactions and neutropenia.

Infusion-Related Reactions
In the majority of patients with NHL, infusion-related reactions consisting of fever, chills/rigors, nausea, pruitus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first rituximab infusion. Infusion-related reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion-related reactions was highest during the first infusion (77%) and decreased with each subsequent infusion [see Warnings and Precautions (5.1)]. In patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of rituximab at Cycle 2, the incidence of Grade 3-4 infusion-related reactions on the day of or day after the 90-minute infusion was 2.8% (95% CI [1.3%, 5.0%]) [see Warnings and Precautions (5.1)].

In randomized, controlled studies where rituximab was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received rituximab. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received rituximab.

Cytopenias and hypogammaglobulinemia
In patients with NHL receiving rituximab monotherapy, NCI-CTCAE Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy occurred during the single-arm studies.

In studies of monotherapy, rituximab-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

In CLL trials, the frequency of prolonged neutropenia and late-onset neutropenia was higher in patients treated with R-F compared to patients treated with FC. Prolonged neutropenia is defined as Grade 3–4 neutropenia that has not resolved between 24 and 42 days after the last dose of study treatment. Late-onset neutropenia is defined as Grade 3–4 neutropenia starting at least 42 days after the last treatment dose.

In patients with previously untreated CLL, the frequency of prolonged neutropenia was 8.5% for patients who received R-F (n=402) and 5.8% for patients who received FC (n=398). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 14.8% in 209 patients who received R-F and 4.3% in 230 patients who received FC.

For patients with previously treated CLL, the frequency of prolonged neutropenia was 24.8% for patients who received R-F (n=274) and 18.1% for patients who received FC (n=274). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 38.7% in 160 patients who received R-F and 13.6% of 147 patients who received FC.

Relapsed or Refractory, Low-Grade NHL
Adverse reactions presented in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of rituximab administered as a single agent. Most patients received rituximab 357 mg/m² weekly for 4 doses.
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Table 1

Incidence of Adverse Reactions in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL. Receiving Single-agent Rituximab (N=356).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 and 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reactions</td>
<td>99</td>
<td>57</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>86</td>
<td>10</td>
</tr>
<tr>
<td>Fever</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Heme and Lympathic System</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Increased Lethargy</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Bronchospasm</td>
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<td>1</td>
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<tr>
<td>Dyspnea</td>
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<td>1</td>
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<tr>
<td>Sinusitis</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>38</td>
<td>3</td>
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<tr>
<td>Angioedema</td>
<td>11</td>
<td>1</td>
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<tr>
<td>Hypergammaglobulinemia</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
<td>32</td>
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</tr>
<tr>
<td>Obstructive</td>
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<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Malaria</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Adverse reactions observed up to 12 months following rituximab.

6.4 Immunoegenicity

As with all therapeutic proteins, there is a potential for immunoegenicity. 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 the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other rituximab products may be misleading.

Using an ELISA assay, anti-rituximab antibody was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent rituximab. Three of the four patients had an objective clinical response. A total of 273/2578 (11%) patients with RA tested positive for anti-rituximab antibodies at any time after receiving rituximab. Anti-rituximab antibody positivity was not associated with increased rates of infusion-related reactions or other adverse events. Upon further treatment, the proportions of patients with infusion-related reactions were similar between anti-rituximab antibody positive and negative patients, and most reactions were mild to moderate. Four anti-rituximab antibody positive patients had serious infusion-related reactions, and the temporal relationship between anti-rituximab antibody positivity and infusion-related reaction was variable. A total of 23/39 (23%) rituximab-treated adult patients with GPA and MPA developed antitumor antibodies at any time after receiving rituximab. Anti-rituximab antibody positivity was not associated with increased rates of infusion-related reactions or other adverse events. Upon further treatment, the proportions of patients with infusion-related reactions were similar between anti-rituximab antibody positive and negative patients, and most reactions were mild to moderate. Four anti-rituximab antibody positive patients who had serious infusion-related reactions, and the temporal relationship between anti-rituximab antibody positivity and infusion-related reaction was variable.
In NHL Study 6, the following adverse reactions were reported more frequently receiving rituximab as single-agent maintenance therapy following rituximab reactions, Grade

In NHL Study 5, detailed safety data collection was limited to serious adverse neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%).

In NHL Study 4, patients in the R-CVP arm experienced a higher incidence in these single-arm rituximab studies, bronchiolitis obliterans occurred *Adverse reactions observed up to 12 months following rituximab.*

**Cardiovascular System**

**Musculoskeletal System**

**Body as a Whole**

**Low-Grade or Follicular NHL, Receiving Single-agent Rituximab (N=356)*, †**

- Myalgia
- Dizziness
- Vomiting
- Nausea
- Pruritus
- Night Sweats
- Anemia
- Thrombocytopenia
- Neutropenia
- Leukopenia
- Throat Irritation
- Back Pain
- Pain
- Asthenia
- ≥ 2% in the rituximab group were infections (4% vs. 1%) and positivity and infusion-related reaction was variable.

With infusion-related reactions were similar between anti-rituximab antibody or other adverse events. Upon further treatment, the proportions of patients positivity was not associated with increased rates of infusion-related reactions antibodies at any time after receiving rituximab. Anti-rituximab antibody A total of 273/2578 (11%) patients with RA tested positive for anti-rituximab products may be misleading.

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and (including neutralizing antibody) positivity in an assay may be influenced. 6.4 Immunogenicity

Patients with previously untreated follicular NHL evaluated in NHL Study 5 were randomized to rituximab as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to rituximab in combination with chemotherapy. Of these, 123 (24%) patients in the rituximab arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of rituximab in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

**Chronic Lymphocytic Leukemia**

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 rituximab-treated patients (35%) were 65 years of age or older; of these, 100 rituximab-treated patients (15%) were 70 years of age or older. In exploratory analyses defined by age, there was no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 70 years of age or older in CLL Study 1 or in CLL Study 2; there was also no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 65 years of age or older in CLL Study 2. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of rituximab. In CLL Study 1, the dose intensity of rituximab was similar in older and younger patients, however in CLL Study 2 older patients received a lower dose intensity of rituximab.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia (44% vs. 31% (CLL Study 1); 54% vs. 39% (CLL Study 2)), febrile neutropenia (18% vs. 6% (NHL Study 10 (NCT00719472))), anemia (5% vs. 2% (CLL Study 1); 21% vs. 10% (CLL Study 2); thrombocytopenia (19% vs. 8% (CLL Study 2), pancytopenia (7% vs. 2% (CLL Study 1); 7% vs. 2% (CLL Study 2)) and infections (30% vs. 14% (CLL Study 2)).

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This brief summary is based on the TRUXIMA full Prescribing Information
dated 05/2020.

RIX-40363 Revised July 2020
From Making Oncology Clinical Pathways Multidisciplinary, to Adding the Patient’s Voice

MARY CAFFREY

THE RISE OF DECISION SUPPORT TOOLS—clinical pathways—in oncology care can allow health systems to create standards for the use of expensive new therapies and identify those physicians who are not following guidelines.

For this reason, payers would seem to embrace pathways. But according to the final panel at Patient-Centered Oncology Care®, that can create a new problem: if each payer tries to impose its own pathways, it’s an administrative and ethical nightmare.

“Clinicians need a moral justification for using pathways—they have to believe that the choices on pathway are the right choices for a patient. So we cannot have different pathways for different payers,” said Kerin Adelson, MD, associate professor and chief quality officer, Smilow Cancer Hospital, Yale School of Medicine.

But Adelson said pathways have been “instrumental” in bringing the doctor and patient together in a shared decision. The burden is on us as clinicians to do a better job with that.”

“We brought back the Moffitt pathways to our cancer center, and then modified them to reflect our local practice patterns,” McKinney said. “Those pathways are truly multidisciplinary—they incorporate medical oncology, surgical oncology, radiation oncology, and life care clinical trials.”

An important feature of the Moffitt pathways, she said, is the incorporation of drug costs. “That was very eye-opening to our medical oncologists when they were looking at 2 different options. They had no idea.”

Initially, the Moffitt pathways were a reference document, and as Roswell Park built its own pathways program, it sought commercial vendors so it could better measure uptake and concordance. Today, it also uses the ClinicalPath system.

Promoting Clinical Trials
Alvarnas said the 4 panelists and himself “represent 5 [National Cancer Institute]-designated Comprehensive Cancer Centers, which may, given the research cores at each of these respective centers, increase the relative complexity of the clinical pathways.

“For lack of a better word,” he said, “academic centers often have a certain inertia associated with them. How have you navigated the challenge of capturing enough complexity regarding clinical trials, as well as getting your physicians to go on the journey?”

Said Fields, “Clinical trials have been a major component of our clinical pathways since the very beginning.” Their multidisciplinary nature has allowed the EHR to give clinicians information about clinical trials. Yes, there is maintenance involved, but the added features allow Moffitt to use pathways to measure quality, cost, and efficiencies, and quickly identify patients eligible for trials—at the point of care.
Adelson said following pathways and getting patients into clinical trials can require commitment and creativity from the research staff. Some of the best stories come from community oncologists, where a general oncologist could not possibly track every open trial, but a reminder from the pathway is the factor that gets their patient enrolled. And when patients are enrolled in trials, there are savings. “The drugs are being billed to the pharmaceutical company, but that really allows academic centers to be successful [under] value-based models,” she said.

Gaining the trust of pathway users is critical, Jackman said. “It’s not just the users being able to see what trials are available and knowing when to send them in. It’s the converse as well, knowing when a trial isn’t available, and allowing folks in the satellites to retain their patients and be able to reassure them. ‘Look, I know what’s going on, and you know, at the campus in Boston, they don’t have a trial for you right now. But here’s what they would do.’”

Pathway developers and users learn from each other. “Learning happens in so many different ways with respect to trials,” he said. Pathway choices, or branching, can both recognize what’s currently available and anticipate what’s coming. For example, in lung cancer the Dana-Farber pathway has branches for EGFR and ALK mutations. “And we put a branch on for KRAS,” even though there’s not yet an FDA-approved agent. But branches can be built to accommodate clinical trials in emerging areas.

The Patient’s Voice
Alvarnas addressed a complaint from physicians that pathways don’t accommodate individual patients, and asked McKinney how this is handled at Roswell Park.

This is an area where there’s a need for more growth, she said. The ClinicalPath platform does “a really good job” at incorporating evidence-based preferences for patients. During the current coronavirus disease 2019 (COVID-19) pandemic, for example, the pathway incorporated subcutaneous therapies to reduce “chair time” from infusions.

But when it comes to patient wishes, the guidelines from the American Society of Clinical Oncology (ASCO) are preferable, McKinney said. “One of the things that ASCO recommends is that patients are involved in the development of pathways. And I don’t know that there’s any commercial vendor that has started to do that.” If cancer centers are using a commercial platform, they should encourage patient involvement in development, but if they are developing internally, it’s on the institution to figure it out: “How can we incorporate our patients into that development and maintenance process, so that we’re getting their voice?”

Roswell Park built a patient education pathway and a young adult pathway, to recognize that this age group often has different outcomes and needs, such as fertility services. “They might be transitioning from Mom and Dad’s insurance and then going on to their own insurance plan,” McKinney said. “Once we get them through treatment, then there’s a whole other issue of survivorship, because they’ve got their whole life to live with potential comorbidities, potential for a secondary cancer. We can really make pathways work for our patients, because that’s who we’re there to serve.”

Adelson has research funding to develop a pathway that is a shared decision-making tool, with the physician seeing an evidence-based pathway. The patient can log in and see the evidence-based options, with differences by adverse effects (AEs). AEs are of varying importance to patients, she said.

“Right now, we are completely neglecting the voice and preferences of the patient, and this is actually an incredible opportunity to bring the doctor and patient together in a shared decision,” Adelson said. “The burden is on us as clinicians to do a better job with that.”

McKinney said patient-reported data could change pathways. If it turns out that only 5% to 7% of patients in the real world can tolerate a certain treatment, “maybe that really shouldn’t be the first choice on a clinical pathway.”

Talking About Cost
Adelson said CMS’ OCM incorporates a requirement of communicating with patients about their care plan, the one instance in which a payer requires this. For the most part, it doesn’t happen, and payers won’t cover shared decision making. Fields agreed, indicating that although payers say they want clinicians to incorporate patient goals, these things aren’t in contracts.

Adelson said: “When we talk about cost, we don’t do a good job about talking about ‘cost to whom?’ So there’s overall cost to society, which is the overall thing that a treatment costs in some ways, but it’s also how much productivity is lost from that member of society who may not be able to work. Then there’s cost to the payer.”

What the payer sees and what the patient “pays” are often not in alignment. Adelson said many breast cancer pathways put patients on paclitaxel weekly for 12 weeks, because it may not require supportive therapy. “But for a patient, that’s an extra 8 visits to the infusion center, it’s potentially an extra 1 to 2 months out of work. And it could mean hiring a babysitter and parking and all sorts of other things that may negatively impact their financial quality of life.”

Jackman agreed that many pathways are focused on drug costs and don’t look at the patient costs in the total cost of care. Dana-Farber has tried to collect this data to share with payers, but Jackman said the conversation is not “where we’d like it to be.”

Challenges with payers involve expectations that pathways are going to solve problems they are not designed to fix. McKinney and Adelson said pathways will never be designed for 100% concordance, because that would mean physicians are not taking individual patient needs into account. Roswell Park researched this issue, and found that 70% of cases handled off pathway were due to toxicity or a comorbidity.

Adelson said pathways are not the final answer to holding down drug costs—drug price reform is required. “Guideline-based treatment is extremely expensive when novel therapies are included,” she said. “If we’re looking at mechanisms to control costs, we’ve got to talk about pharmaceutical pricing.”

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Verzenio + AI (ITT PFS analysis: HR=0.540 [95% CI: 0.418-0.698]; N=493): treatment-free interval <36 months (exploratory PFS analysis: HR=0.441 [95% CI: 0.241-0.805]; n=76) and liver metastases (exploratory PFS analysis: HR=0.477 [95% CI: 0.272-0.837]; n=78). Verzenio + fulvestrant (ITT PFS analysis: HR=0.553 [95% CI: 0.449-0.681]; N=669): primary resistance (preplanned PFS analysis: HR=0.454 [95% CI: 0.306-0.674]; n=169) and visceral disease (preplanned PFS analysis: HR=0.481 [95% CI: 0.369-0.627]; n=373). The analyses were not adjusted for multiplicity and the study was not powered to test the effect of Verzenio + AI/fulvestrant among subgroups. Verzenio single-agent (ITT ORR analysis: 19.7% [95% CI: 13.3-27.5%]; progression on or after ET and prior chemotherapy in the metastatic setting and visceral disease.

For additional information and full trial design, see verzenio.com/hcp/efficacy.

Verzenio is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced or metastatic breast cancer (MBC):• In combination with fulvestrant for women with disease progression following endocrine therapy• In combination with an aromatase inhibitor (AI) for postmenopausal women as initial endocrine-based therapy• As a single agent for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

Select Important Safety Information

Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection. Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 was 11 and 18 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1. Instruct patients that at the first sign of loose stools, they should start anti-diarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Neutropenia occurred in 4% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 4% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 27% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days. Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in 5% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors.
Select Important Safety Information

Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.

Grade ≥3 increases in alanine aminotransferase (ALT) (6% versus 2%) and aspartate aminotransferase (AST) (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 2.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential hepatotoxicity, monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause fetal harm when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Discover an option for HR+, HER2- MBC patients at verzenio.com/hcp

Select Important Safety Information (cont’d)

The most common adverse reactions (all grades, ≥10%) observed in MONARCH 3 for Verzenio plus anastrozole or letrozole and ≥2% higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole were diarrhea (81% vs 30%), neutropenia (41% vs 2%), fatigue (40% vs 32%), infections (39% vs 29%), nausea (39% vs 20%), abdominal pain (29% vs 12%), vomiting (26% vs 12%), anemia (28% vs 5%), alopecia (27% vs 11%), decreased appetite (24% vs 9%), leukopenia (21% vs 2%), creatinine increased (19% vs 4%), constipation (16% vs 12%), ALT increased (16% vs 7%), AST increased (15% vs 7%), rash (14% vs 5%), pruritus (13% vs 9%), cough (13% vs 9%), dyspnea (12% vs 6%), dizziness (11% vs 9%), weight decreased (10% vs 3%), influenza-like illness (10% vs 8%), and thrombocytopenia (10% vs 2%).

The most common adverse reactions (all grades, ≥10%) observed in MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were diarrhea (66% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The most common adverse reactions (all grades, ≥10%) observed in MONARCH 1 with Verzenio were diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), neutropenia (37%), vomiting (35%), infections (31%), anemia (25%), thrombocytopenia (20%), headache (20%), cough (19%), leukopenia (17%), constipation (17%), arthralgia (15%), dry mouth (14%), weight decreased (14%), stomatitis (14%), creatinine increased (13%), alopecia (12%), dysgeusia (12%), pyrexia (11%), dizziness (11%), and dehydration (10%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 3 were neutropenia (22% vs 2%), diarrhea (9% vs 1%), leukopenia (8% vs <1%), ALT increased (7% vs 2%), and anemia (6% vs 1%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 2 were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), and infections (6% vs 3%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions from MONARCH 1 with Verzenio were neutropenia (24%), diarrhea (20%), fatigue (13%), infections (7%), leukopenia (6%), anemia (5%), and nausea (5%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 3 in ≥10% for Verzenio plus anastrozole or letrozole and ≥2% higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole were increased serum creatinine (58% vs 84%, 2% vs 0%), decreased white blood cells (82% vs 27%, 13% vs <1%), anemia (82% vs 26%, 2% vs 0%), decreased neutrophil count (80% vs 21%, 22% vs 3%), decreased lymphocyte count (53% vs 26%, 5% vs 2%), decreased platelet count (36% vs 12%, 2% vs <1%), increased ALT (48% vs 25%, 7% vs 2%), and increased AST (37% vs 23%, 4% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 3 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were increased serum creatinine (98% vs 84%, 2% vs 0%), decreased white blood cells (90% vs 33%, 23% vs 1%), decreased neutrophil count (87% vs 30%, 33% vs 4%), anemia (84% vs 33%, 3% vs <1%), decreased lymphocyte count (63% vs 32%, 12% vs 2%), decreased platelet count (53% vs 15%, 2% vs 0%), increased ALT (41% vs 32%, 5% vs 1%), and increased AST (37% vs 25%, 4% vs 4%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (98% <1%), decreased white blood cells (91% 28%), decreased neutrophil count (88% 27%), anemia (68% 0%), decreased lymphocyte count (42% 14%), decreased platelet count (41% 2%), increased ALT (31% 3%), and increased AST (30% 4%).

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. Co-administration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with severe renal impairment (ClCr <30 mL/min) end stage renal disease, or in patients on dialysis is unknown. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and renal impairment (ClCr ≥30-89 mL/min).

AL HCP: SI 17SEP2019

Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.

References:

PP-AL-US-2073-D 12.2019 C Lilly USA, LLC. 2019. All rights reserved. Verzenio® is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries or affiliates.
Embry-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and hold at least 2 weeks after the last dose.

ADVERSE REACTIONS

Clinical Studies 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.

MONARCH 3 (VERZENIO in Combination with an Aromatase Inhibitor [Anastrozole or Letrozole] as Initial Endocrine-Based Therapy)

Postmenopausal Women with HR-positive, HER2-negative, locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician’s choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus aromatase or letrozole. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 13% of patients receiving VERZENIO plus an aromatase inhibitor compared to 2% of patients receiving placebo plus an aromatase inhibitor. VERZENIO dose reductions due to neutropenia of any grade occurred in 11% of patients receiving VERZENIO plus an aromatase inhibitor compared to 0.6% of patients receiving placebo plus an aromatase inhibitor.

Permanent treatment discontinuation due to an adverse event was reported in 13% of patients receiving VERZENIO plus an aromatase inhibitor and in 3% placebo plus an aromatase inhibitor. Adverse reactions leading to permanent treatment discontinuation for patients receiving VERZENIO plus an aromatase inhibitor were diarrhea (2%), ALT increased (2%), infection (1%), venous thromboembolic events (VTE) (1%), neutropenia (0.9%), renal impairment (0.9%), AST increased (0.6%), dyspnea (0.6%), pulmonary fibrosis (0.6%) and anaemia, rash, weight decreased and thrombocytopenia (each 0.3%).

Deaths during treatment or the 30-day follow-up, regardless of causality, were reported in 11 cases (3%) of VERZENIO plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving VERZENIO plus an aromatase inhibitor included: (3%) patient deaths due to underlying disease, (3% (0.9%) due to lung infection, (3% (0.9%) due to VTE event, (1%) due to febrile neutropenia, and (1%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm and ≤2% than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leucopenia (Table 1). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anaemia. Diarrhea incidence was greatest during the first month of VERZENIO dosing. The median time to onset of the first diarrhoea event was 8 days, and the median duration of diarrhoea from first event was 4 days. Two deaths were reported in patients with diarrhoea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhoea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhoea were similar across MONARCH 3, MONARCH 2 and MONARCH 1.

Monitor complete blood counts prior to the start of VERZENIO therapy, every week for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Table 1: Adverse Reactions ≥1% of Patients Receiving VERZENIO Plus Anastrozole or Letrozole and >2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO plus Anastrozole or Letrozole N=327</th>
<th>Placebo plus Anastrozole or Letrozole N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grade 3 %</td>
<td>Grade 4 %</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>39</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26</td>
<td>7</td>
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<tr>
<td>Neutropenia</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>2</td>
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<tr>
<td>Influenza like Illness</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Verzenio® (abemaciclib) tablets, for oral use
due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one/uni00A0(0.2%) due to cerebral infarction.

Additional adverse reactions in MONARCH 3 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, and pelvic venous thrombosis), which were reported in 5% of patients treated with VERZENIO plus anastrozole or letrozole as compared to 0.6% of patients treated with anastrozole or letrozole plus placebo.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST increased</td>
<td>30</td>
<td>4</td>
<td>0</td>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
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<tr>
<td>Neutrophil count decreased</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>82</td>
<td>2</td>
<td>0</td>
<td>82</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>80</td>
<td>19</td>
<td>2</td>
<td>80</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>50</td>
<td>25</td>
<td>&lt;1</td>
<td>50</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>&lt;1</td>
<td>0</td>
<td>11</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Laboratory Abnormalities >10% in Patients Receiving VERZENIO Plus Anastrozole or Letrozole and <24% Higher Than Placebo Plus Anastrozole in MONARCH 3

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine increased</td>
<td>98</td>
<td>2</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>0</td>
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<tr>
<td>White blood cell decreased</td>
<td>82</td>
<td>13</td>
<td>0</td>
<td>27</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>82</td>
<td>2</td>
<td>0</td>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>80</td>
<td>19</td>
<td>2</td>
<td>21</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>50</td>
<td>25</td>
<td>&lt;1</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
<td>12</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia min transfr increased</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic transfr increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>23</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

For the treatment of patients with advanced hormone receptor–positive, HER2-negative breast cancer, VERZENIO is indicated for use as a monotherapy in women who have not received prior endocrine therapy and for use as combination therapy with fulvestrant in women who have received prior endocrine therapy.

<table>
<thead>
<tr>
<th>Gastrointestinal Disorders</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>86</td>
<td>13</td>
<td>0</td>
<td>25</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>3</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Abdominal Pain</td>
<td>35</td>
<td>2</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>&lt;1</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15</td>
<td>&lt;1</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>43</td>
<td>9</td>
<td>&lt;1</td>
<td>25</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>46</td>
<td>24</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions >10% in Patients Receiving VERZENIO Plus Fulvestrant and <24% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine increased</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>82</td>
<td>13</td>
<td>0</td>
<td>27</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>82</td>
<td>2</td>
<td>0</td>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>80</td>
<td>19</td>
<td>2</td>
<td>21</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>50</td>
<td>25</td>
<td>&lt;1</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
<td>12</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia min transfr increased</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic transfr increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>23</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 4: Laboratory Abnormalities >10% in Patients Receiving VERZENIO Plus Fulvestrant and <24% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine increased</td>
<td>86</td>
<td>1</td>
<td>0</td>
<td>74</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>90</td>
<td>23</td>
<td>&lt;1</td>
<td>33</td>
<td>&lt;1</td>
<td>&lt;1</td>
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<tr>
<td>Neutrophil count decreased</td>
<td>87</td>
<td>29</td>
<td>4</td>
<td>30</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>84</td>
<td>3</td>
<td>0</td>
<td>77</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>63</td>
<td>12</td>
<td>&lt;1</td>
<td>32</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>53</td>
<td>&lt;1</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia min transfr increased</td>
<td>41</td>
<td>4</td>
<td>&lt;1</td>
<td>32</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic transfr increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>4</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 5: Laboratory Abnormalities >10% in Patients Receiving VERZENIO Plus Fulvestrant and <24% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine increased</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>90</td>
<td>23</td>
<td>&lt;1</td>
<td>33</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>87</td>
<td>29</td>
<td>4</td>
<td>30</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>84</td>
<td>3</td>
<td>0</td>
<td>77</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>63</td>
<td>12</td>
<td>&lt;1</td>
<td>32</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>53</td>
<td>&lt;1</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia min transfr increased</td>
<td>41</td>
<td>4</td>
<td>&lt;1</td>
<td>32</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic transfr increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>4</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 6: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST increased</td>
<td>30</td>
<td>4</td>
<td>0</td>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anaplastic transfr increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 7: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
<td>36</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
<td>46</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anaplastic transfr increased</td>
<td>37</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
The most common adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 5). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

Table 5: Adverse Reactions (≥10% of Patients) in MONARCH 1

<table>
<thead>
<tr>
<th>Category</th>
<th>VERZENIO Plus Fulvestrant</th>
<th>Placebo Plus Fulvestrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>90%</td>
<td>20%</td>
</tr>
<tr>
<td>Nausea</td>
<td>64%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>39%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>17%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>65%</td>
<td>13%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37%</td>
<td>19%</td>
</tr>
<tr>
<td>Anemia</td>
<td>52%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>45%</td>
<td>3%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Depression</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>13%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>14%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Definitions:
a. Includes asthenia, fatigue.
b. Includes neutropenia, neutrophil count decreased.
c. Includes anemia, hemoglobin decreased, hemoglobin decreased, red blood cell count decreased.
d. Includes platelet count decreased, trombocytopenia.
e. Includes leukopenia, white blood cell count decreased.

Creatinine increased
Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

Drug Interactions

Effect of Other Drugs on VERZENIO
CYP3A inhibitors
Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoneconazole
Avoid concomitant use of ketoneconazole. Ketoneconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors
In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 5-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.

Moderate CYP3A inhibitors
With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg increments, if necessary.

Strong and Moderate CYP3A inducers
Co-administration of strong or moderate CYP3A inducers decreases the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

Use in Specifc Populations

Pregnancy
Risk Summary
Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (see Data). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data
Animal Data
In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses >4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sterna, bipartite ossification of thoracic centrum, and rudimentary or medullated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Lactation
Risk Summary
There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing
Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception
Female
VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility
Males
Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.

Pediatric Use
The safety and effectiveness of VERZENIO have not been established in pediatric patients.

Geriatric Use

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehiscence, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr >30–89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

Overdosage

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.

Additional information can be found at www.VERZENIO.com.
WITH UNPRECEDENTED PROGRESS In cancer treatments, cancer is evolving into a chronic disease, and more novel therapies are being introduced as the cost of health care receives greater focus. As a result, federal policy decisions are being made that shape oncologists’ ability to deliver cancer care, said Debra Patt, MD, PhD, MBA, executive vice president of policy and strategic initiatives at Texas Oncology.

During her featured session at The American Journal of Managed Care®’s Patient-Centered Oncology Care® meeting, Patt discussed the current landscape of cancer care delivery, trends in drug pricing, alternative payment models, and more.

Health care costs as a percentage of gross domestic product continue to increase in the United States and are already higher than in any other country, Patt pointed out. That increase translates to higher out-of-pocket costs for patients and higher premium contributions by employers to health plans. “Regardless of the value, know that the increase in cost is not sustainable,” she said.

Access to care continues to be a critical issue made more important through challenges to the Affordable Care Act (ACA) and the uneven expansion of Medicaid. And when the coronavirus disease 2019 (COVID-19) pandemic hit, it quickly became apparent that patients with advanced cancer had higher mortality rates from COVID-19, “but no one thought of the secondary consequences,” she said.

Since the onset of the COVID-19 pandemic, places that conduct screenings have reduced capacity and patients are fearful to go into the doctor’s office to get crucial cancer screenings. As a result, screenings are down by as much as 80%, and there are delays in diagnosis.

“This is something really important as we think about patient-centered oncology care—people need to get screened, and they need to see their doctors in order to make sure that their symptoms don’t go unnoticed,” Patt said. “Because when we can diagnose cancer early, it’s the best opportunity that we have to cure cancer.”

There are a number of relevant executive orders on drug pricing, including one on rebates to make prices lower by eliminating kickbacks to middlemen; one that allowed for drugs to be imported from Canada; and one to change the mechanism of 340B reimbursement as it pertains to insulin and epinephrine. Another executive order around which significant uncertainty remains is the so-called International Pricing Index (IPI), which was first announced in 2018.

After it was introduced, nothing happened with the IPI until September 2020 when President Donald Trump announced the Most Favored Nation Price executive order for Medicare Part B and Part D drugs. Under the plan, HHS would create a program through which Medicare paid no more for drugs than the lowest price paid by countries in the Organization for Economic Cooperation and Development. However, the details remain unclear, Patt said. For instance, it’s not clear which drugs will be included or how quickly a pilot might be implemented.

“So I think that when we look at health care policy changes, abrupt and sudden changes that are drastic to the system [make it] very challenging for the system to continue to operate effectively,” she said. “And I will say that oncology care delivery does happen very effectively.”

Changing how finances are managed is an interest that the current administration shares with its predecessor. The Oncology Care Model (OCM) launched in 2015 under the Obama administration and has been extended through 2021; a successor called Oncology Care First has been discussed for 2022, but details are not final.

Although the early results of the OCM didn’t demonstrate “a tremendous amount of cost savings,” Patt believes that “the jury is still out.” In addition, CMS isn’t the only entity interested in alternative payment models, as more pilots are popping up in the commercial space.

“I can say my practice alone has 5 alternative payment model pilots with commercial payers, and they mirror many aspects of the OCM,” she said. “So, as we try to make the walk from volume to value in oncology, I think alternative payment model pilots are a really important way to do that.”

The Center for Medicare and Medicaid Innovation also finalized the Radiation Oncology Model (ROM); however, since Patt gave her talk, CMS announced it will delay the model until July 1, 2021. The ROM uses episode-based payments for radiation oncology and includes physician group practices, freestanding radiation centers, and hospital outpatient departments. The model includes several payment episodes for 16 cancer types.

The challenge of the ROM, compared with the OCM, is that the ROM is mandatory for one-third of ZIP codes. A mandatory pilot is always difficult, but especially so during a time when “cancer care is suffering quite a bit,” Patt said.

The growth of biosimilars is also a very important part of cancer care, as biosimilars allow for a switch from an innovator product. However, many biosimilars entering the market at one time presents a challenge, as insurance companies will tend to pick and choose among the biosimilars. The result can be that different insurance companies’ requirements dictate that a given practice use different biosimilars of the same innovator product, depending on the patient’s coverage.

Finally, Patt highlighted that the election outcome may impact health care. The Trump administration’s main focus has been to cut prescription drug prices (at press time, there was more activity in this area). However, Patt believes that the Biden campaign “actually has a real focus on health care.” Speaking 5 weeks before the election, she said now President-elect Joe Biden also wants to deal with prescription drug prices, but his focus has been on access to care and providing a public health option for all.

“So, I think whether Trump remains in the White House, or Biden is elected to the White House, drug pricing [and] cancer care will be center stage, and health care will be a central focus of the election and of the next presidency,” Patt said.

**REFERENCES**


PHARMACY BENEFIT MANAGERS (PBMs), once just administrators created to ease claims processing, have grown to a position of power that comes with conflicts of interest aplenty.

Today, pharmacies and consumers alike encounter pitfalls, such as spread pricing, the use of rebate aggregators, and threats of drugs being removed from formularies. All this makes dealing with PBMs an unfortunate reality for drug manufacturers and pharmacies, and for patients who depend on the drugs that PBMs control, said a panel of experts at Patient-Centered Oncology Care® 2020.

The discussion was moderated by meeting Cochair Joseph Alvarnas, MD, vice president of government affairs, senior medical director for employer strategy, and clinical professor, City of Hope, and editor-in-chief, Evidence-Based Oncology®. The panel included Ray Bailey, BPharm, RPh, vice president of pharmacy, Florida Cancer Specialists; Antonio Ciaccia, chief strategy officer at 3 Axis Advisors; Jonathan E. Levitt, JD, attorney and founding partner at Frier Levitt; and Denise Giambalvo, MS, vice president of Midwest Business Group on Health.

The root of the problem with PBMs, Ciaccia explained at the start of the discussion, is the way their role has shifted. At first, their purpose was to allow health care benefits providers to leverage better drug prices. Now, he said, PBMs have essentially become the pharmacies themselves rather than just the middleman.

This then leads to the question of whether PBMs have any incentive to control drug costs when they have become part of that cost. And with the way things are going, it has become apparent that they lack any cost-control incentive, at least as far as the panelists can see. PBM practices, including spread pricing and demanding bigger rebates from manufacturers to keep their products on formulary, actually drive up drug prices, an issue that affects the entire health care system.

"[PBMs] have a profit incentive to keep the prices high, and work to discount off that price. So, if prices were low, we wouldn't really need the PBMs as much as we need them today," Ciaccia said. "Plan sponsors, big and small, all need somebody to come in and knock down those prices. So, [PBMs] are basically the arsonist and the firefighter into one."

One way that PBMs have capitalized on their position is spread pricing, in which they keep a portion of the amount billed to health plans for prescription drugs instead of passing that money on to the pharmacies.

Ciaccia recalled a situation in which pharmacies within the Ohio Medicaid managed care plan saw a 60% to 80% decrease in their gross margins. The state auditor later discovered that there was $244 million in spread pricing by PBMs, and the spread had been growing over time.

Levitt raised the issue of language in contracts. Plan sponsors get rebate checks according to their agreements with PBMs, but clever wording can allow PBMs to withhold extra manufacturer rebate money.

Giambalvo explained that for employers and plan sponsors to protect themselves, there needs to be specific, clear contract language. "You can't just say ‘rebates’—you have to say, ‘all administrative fees received from the manufacturer,’” she stressed. "Go back to the employer, so that everything is incorporated.”

Another problem Levitt raised is rebate aggregators, which PBMs sometimes hire to collect the rebates they get from manufacturers for including their drugs in the PBM’s formulary.

The issue is that many rebate aggregators are owned by or affiliated with the very PBMs that employ them.

A Medicare plan retained by Levitt’s firm audited a PBM suspected of keeping extra money, and this issue was brought to light.

"What the plan didn’t know was that the PBM owned a rebate aggregator,” Levitt explained. “That rebate aggregator collected all the dollars, and it only gave about 40% of those dollars to the PBM. The PBM [contract] said, ‘We’re going to give you 90%, and we’re going to keep 10%.’ But what they failed to reveal was that the PBM rebate aggregator had sucked 62% of the money out the system.”

Self-insured employers also have rights that they need to know and take advantage of to avoid running into similar issues, according to Giambalvo. These employers can carve out pieces and create their own pharmacy network that they can direct-contract with, she said.

“Another really important piece is using an independent pharmacy and therapeutics committee, so that the [formulary] decisions are not being influenced by the rebates that are received,” Giambalvo noted. Oncology drugs that are not showing good outcomes have no place in formularies, so it’s important for employers or plan sponsors to know what they are paying for. In the long run, using more effective drugs will reduce total spending, she said.

Giambalvo and Levitt stated the importance of having consultants with a high level of expertise look over contracts, and both stressed that consultants should be independent. Employers and payers should be aware that many consultants are paid by PBMs.

As Alvarnas pointed out, jumping through hoops to get fair deals from the payer and pharmacy perspectives should not be necessary, and it points to a system in need of an overhaul.

Providers see direct effects on patients that arise from working in a system with PBMs. In oncology, where drugs are constantly evolving and are very expensive, Bailey sees patients face barriers to care due to rising prices and cost shifts to higher co-pays and deductibles for patients.

“We try every day to keep up with all the changes in oncology and all the new drugs, but our patients face immense financial toxicities with drugs that are run through this pharmacy benefits space,” Bailey said. He noted that especially with oral therapies, the first adjudication of a $10,000- or $15,000-per-month drug will typically hit the deductible size of a medical plan.

Bailey’s medically integrated pharmacy at Florida Cancer Specialists mitigates high costs for patients by using value-based models in which it takes on risk for oral drugs the same way it does with intravenous drugs. The pharmacy also keep tabs on in-home supplies to avoid prescribing drugs that will go to waste.

Overall, panelists concluded that change needs to happen. But what that change is remains to be seen. Payers and employers working to better understand contracts, actively calling for audits of PBMs, working toward public policy that fosters transparency, and challenging abusive tactics from PBMs are all steps that could lead to progress.

“We talk a lot in health care about the desired move to value-based care, which is paying a good price for quality care for a patient,” Ciaccia said. “But I challenge people to ask themselves, how can you pay for value if you don’t know what you bought, whether or not it was done at a fair price, or really what the price was in the first place?”
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