Lung Cancer Pioneer Takes Collaborative Approach to Care

PEER EXCHANGE
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CLINICAL CHATS
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FROM THE PHYSICIAN’S DESK
Biologic Aging in BREAST CANCER
By Hyman B. Muss, MD; and Andrew B. Smitherman, MD, MSc

CLINICAL PERSPECTIVES
Daniel P. Petrylak, MD, Discusses Immunotherapeutic Agents in UROTHELIAL CANCER

Smoking Cessation Support Plays a Vital Role in Improving Lung Cancer Screening
By Matthew A. Steliga, MD

Roy S. Herbst, MD, PhD

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24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.\textsuperscript{1,2}

### 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 hemarthrosis 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 antplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antplatelet 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 opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 25% 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 cytopenies, 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.
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.

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).

**DRUG INTERACTIONS**

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

**SPECIFIC POPULATIONS**

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

**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.

**REFERENCES**


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

Learn more at BRUKINSA.com
Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 62.
The Chance to Make a Difference
Made Herbst a Lung Cancer Pioneer

by JASON HARRIS

At the forefront of innovation in the treatment of patients with lung cancer, investigator Roy S. Herbst, MD, PhD, favors a collaborative approach to drug development and clinical strategies. Herbst will bring that spirit to the 22nd Annual International Lung Cancer Congress® (ILCC) hosted by Physicians’ Education Resource®, LLC (PER®) on July 29 to 31.

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DEPARTMENTS

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Adaptive Trial Design Fuels Precision Medicine Efficacy

BIOMARKER-DRIVEN CLINICAL TRIAL designs are woven so thoroughly into the fabric of oncology research today that it’s easy to forget that these once-innovative studies had to prove their value. This is in part thanks to early work of investigators who developed protocols, such as the BATTLE clinical trial program, which was launched for patients with lung cancer 15 years ago.¹

Using an adaptively randomized design, investigators demonstrated that patients could be assigned to treatment with a molecularly targeted therapy that matched aberrations identified through tumor profiling in real time. The findings showed that precision medicine could effectively and efficiently guide therapy.

Similarly, in the past decade, Lung-MAP, a master screening protocol for patients with advanced non–small cell lung cancer, which is active at over 700 institutions, aims to match patients with appropriate therapies—substudies either investigating drugs that target present alterations or evaluating an immunotherapy combination in those without a match—based on the genomic makeup of their tumors.²

The construction of these protocols and trial schema opens up a landscape that was once limited to patients who received testing at the time of diagnosis and no further. Adapting the field to include repeat screening and the use of novel markers such as tumor mutational burden and circulating tumor DNA (ctDNA) set the stage for the next wave of precision medicine discoveries.

For example, investigators analyzed paired data for tissue and plasma ctDNA in 129 patients who underwent Lung-MAP screening. Of these, 52 had oncogenic drivers detected in tissue, of which 43 were also observed in ctDNA, with 9 found in tissue only, for a ctDNA driver sensitivity of 83% (95% CI, 74%-93%). Of the 77 patients with no drivers in tissue, 2 drivers were detected in ctDNA (EGFR exon 20 insertions, MET amplification) for a ctDNA specificity of 97% (95% CI, 91%-100%).³ Results support the use of ctDNA as a determinant of trial eligibility, expanding on the already standard use of a tissue-based next-generation sequencing used in the protocol.

One of the architects of the BATTLE and Lung-MAP programs was Roy S. Herbst, MD, PhD, who is profiled in our cover story in this issue of OncologyLive®. Herbst, alongside fellow trial innovator David R. Gandara, MD, the 2017 Giant of Cancer Care® winner in lung cancer, will chair the 22nd Annual International Lung Cancer Conference® in July, sponsored by Physicians’ Education Resource® LLC (PER®). As in past years, the meeting will synthesize the latest data on targeted agents, immunotherapy, surgery, and radiation oncology in the lung cancer space. The agenda is set to explore, through interactive case discussions, how targeted agents and the expanding array of oncogenic drivers could shape the future of lung cancer therapy in clinical practice.

To find more information, register, and explore PER®’s robust menu of offerings, visit gotoper.com.

As always, thank you for reading,
Mike Hennessy Sr
Chairman and Founder

REFERENCES
FIGHT ON with ONIVYDE®

The first and only FDA-approved treatment, in combination with 5-FU/LV, for metastatic pancreatic cancer after gemcitabine-based therapy, proven to extend overall survival (OS)†

INDICATION
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

WARNINGS AND PRECAUTIONS

Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE + 5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE + 5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset ≥24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE + 5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE + 5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

ADVERSE REACTIONS

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm were diarrhea (any 59%, 26%; severe 13%, 4%), late diarrhea (any 30%, 15%; severe 3%, 0%), fatigue/asthenia (any 43%, 17%; severe 9%, 4%), nausea (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%;...
ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST-GEMCITABINE METASTATIC PANCREATIC CANCER**

FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE¹

• Proven in combination with 5-FU/LV in NAPOLI-1—the largest phase 3 trial¹ in patients with metastatic pancreatic cancer with disease progression after gemcitabine-based therapy.¹,²,³,⁴


For more information, visit ONIVYDEinfo.com
ONIVYDE® (irinotecan liposome injection) for intravenous use

Initial U.S. Approval: 1996

BRIEF SUMMARY: refer to full Prescribing Information for complete product information.

1. INDICATIONS AND USAGE

ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas following gemcitabine-based therapy.

5.1 Severe Neutropenia:

ONIVYDE® is contraindicated in patients with a history of severe neutropenia and a neutrophil count below 1500/mm² or those with a history of severe or life-threatening neutropenia. Monitor blood cell counts periodically during treatment. (see Dosing and Administration 2.2, 5.1)

Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. (see Dosing and Administration 2.2, see Warnings and Precautions 5.2)

4 CONTRAINDICATIONS

ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia: ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosing and Administration, 2.2).

5.2 Severe Diarrhea: ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction (see Cholinergic Reactions, 6.1). An individual patient may experience both early- and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose (see Dosage and Administration, 2.2).

5.3 Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatalILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1).

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia (see Warnings and Precautions, 5.1: Boxed Warning)
- Severe Diarrhea (see Warnings and Precautions, 5.2: Boxed Warning)
- Interstitial Lung Disease (see Warnings and Precautions, 5.3)
- Severe Hypersensitivity Reactions (see Warnings and Precautions, 5.4)

6.1 Clinical Trials Experience

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and S-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/S-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and S-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (S-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dl, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/S-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the S-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/S-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/S-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/S-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® in patients who have experienced a severe or life-threatening neutropenic fever or sepsis (see Clinical Studies, 14) which occurred in 3% and severe or life-threatening neutropenia occurred in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving ONIVYDE®/5-FU/LV monotherapy. The most common adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, neutropenic fever/neutropenic sepsis, nausea, pyrexia, sepsis, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and diarrhea.

### Table 2: Adverse Reactions with Higher Incidence (≥5% Difference for Grades 1–4 or ≥2% Difference for Grades 3–4) in the ONIVYDE®/5-FU/LV Arm

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE®/5-FU/LV n=117</th>
<th>5-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Late diarrhea‡</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>34</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis●</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Intravenous catheter-related infection</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
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<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Dehydration</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

*NCI CTCAE v4.0.
†Early diarrhea: onset ≤24 hours of ONIVYDE® administration.
‡Late diarrhea: onset >1 day after ONIVYDE® administration.
●Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.

**Cholinergic Reactions:** ONIVYDE® can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE®-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea. **Infusion Reactions:** Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE® administration, were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV.

The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥2% difference Grades 3–4 [severe] according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/5-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. **Hematology:** anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). **Hepatic:** increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%). **Metabolic:** hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%). **Renal:** increased creatinine (any 18%, 13%; severe 0%, 0%).

## 7 DRUG INTERACTIONS

### 7.1 Strong CYP3A4 Inducers:
Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifampicin, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

### 7.2 Strong CYP3A4 or UGT1A1 Inhibitors:
Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE® with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, neflnavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy, Risk Summary:
Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

#### 8.2 Lactation, Risk Summary:
There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk (see Data in the full Prescribing Information).

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE®, advise a nursing woman not to breastfeed during treatment with ONIVYDE® and for 1 month after the final dose.

#### 8.3 Females and Males of Reproductive Potential, Contraception, Females:
ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations, 8.1). Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month after the final dose. **Males:** Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE® and for 4 months after the final dose (see Nonclinical Toxicology, 13.1).

#### 8.4 Pediatric Use:
Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

#### 8.5 Geriatric Use:
Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/5-FU/LV in Study 1, 49% were ≥65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

### 10 OVERDOSE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE®.

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ONV-US-000709 V2.0
Reaching Conclusions From Limited Data Holds Pitfalls

by MAURIE MARKMAN, MD

These are most interesting and complex days in the continuing evolution of the COVID-19 pandemic. On one hand, in the United States and a number of other countries, mass vaccination strategies have finally begun to have a major impact on the incidence and severity of infections, with a substantial proportion of the adult population being fully or at least partially vaccinated.

Further, success with the production of several vaccine products in the United States has enabled federal and state government officials to declare that vaccination should be available for all adults, at least in theory, although perhaps not necessarily with the required vaccine supply in specific regions. And plans are underway to initiate widespread vaccinations of adolescents, likely to be followed later this year or early next year by children. This is a critically relevant development as variants continue to become widespread within the population.1

Unfortunately, in many countries the availability of COVID-19 vaccines has been highly problematic and the situation in the developing world is particularly dire. Case numbers in many countries continue to rise as concern about the impact of variants on infectivity and the severity of illness heightens. Added to these major issues is the finding that certain vaccine products appear to be associated with a very small—perhaps 1 in a million—but highly clinically relevant risk of serious, even fatal, blood clots.2,3

Considering the extremely rare nature of these events, investigators have had difficulty characterizing what has been observed except to say the clots have been seen in women between the ages of 18 and 59 years (median, 37 years) and the events are associated with low platelet counts.2 Finally, this analysis is made more complex by knowledge that a diagnosis of a COVID-19 infection itself substantially increases the risk of blood clots.4

International and national public health agencies as well as leading academics around the world have struggled in very real time and in full view of the public to explain what is occurring, how these events might be predicted and prevented, and, ultimately, successfully treated. Under nonpandemic circumstances, discussions and deliberations regarding vaccine safety and efficacy by these agencies and experts would likely have been conducted outside public view with the ability to obtain additional essential information over time before definitive decisions must be made. This will hopefully be the case as novel vaccines are developed to prevent future pandemics, including events associated with other coronaviruses.5

REAL-WORLD EXPERIENCE

The challenges of assessing COVID-19 vaccines shows that events in the real world may differ from those of a formal objective scientific analysis, especially in a setting where such evaluations of necessity involve very small numbers.

As of press time, health agencies in the United States and Europe have reasonably concluded that the benefits of vaccination outweigh the potential risk of serious—even fatal—blood clots, considering the seriousness of a COVID-19 infection, including the risks posed by new and evolving variants.2,4 Based on existing data, it is difficult to disagree with these decisions.

However, from the perspective of specific individuals considering receiving a COVID-19 vaccine, the actual potential for becoming infected with COVID-19 and, most importantly, experiencing a serious infection is essentially unknown, whereas for the person who develops a major blood clot, regardless of how rare this event may be, the risk of severe complications is 100%. Further, younger individuals (for example, those 40 years and younger) appear to have a higher risk of developing a blood clot.
From the Editor

from certain COVID-19 vaccines and a lower risk of experiencing a serious COVID-19 infection than older people.

The point here is that although formal statistical evaluation is very relevant, such analyses must be viewed against a background of views and interpretations that involve individuals in the real world who will inquire about how the evaluation pertains to them. And as the numbers available to draw statistical conclusions become smaller, the ability to draw scientifically valid and clinically meaningful conclusions will decrease.

Although this discussion of a rare toxicity from COVID-19 vaccination is certainly not directly relevant in the cancer arena, the use of statistical tools involving very small numbers can be an equally meaningful and concerning issue.

Consider, for example, a report in an oncology journal that sought to assess the impact of complementary medicine (CM) on cancer-specific outcomes through an analysis based on very small numbers. This evaluation included 1,901,815 individuals in the National Cancer Database who received diagnoses between January 1, 2004, and December 31, 2013, of nonmetastatic breast, lung, prostate, or colorectal cancers. Investigators found a total of 258 patients who reported that they used CM techniques, defined as “other-unproven: cancer treatments administered by nonmedical personnel” in addition to standard therapeutic strategies.

The investigators attempted to match patients in the larger database with these 258 individuals. They concluded that “patients who received CM were more likely to refuse additional conventional cancer treatment and had a higher risk of death” than those who did not use CM. This conclusion was reached with an at-risk population of CM believers that made up 0.0001% of the entire study population.

It is relevant to note the public health care agencies and experts in the epidemiology of vaccine use were very careful to not overly generalize their conclusions, knowing they were dealing with very limited patient numbers. Unfortunately, such caution did not appear to be relevant to the investigators and reviewers of the CM study. Perhaps investigators in all disciplines can learn something of importance from their academic colleagues in the vaccine arena.

REFERENCES

FDA DIGEST

ODAC Upholds 4 of 6 Accelerated Approvals Following Review

The FDA’s Oncologic Drugs Advisory Committee (ODAC) has voted to uphold 4 of 6 accelerated approvals for immunotherapy agents that failed to reach efficacy thresholds for statistical significance for key end points in confirmatory clinical trials.

The decisions were made over the course of a 3-day special hearing as the companies developing the drugs and their physicians cited the long durations of response that many of the agents have exhibited and the unmet treatment need they could potentially fill.

Pembrolizumab (Keytruda) had 3 indications under review. In an 8 to 0 vote, ODAC maintained the accelerated approval of the PD-1 inhibitor as monotherapy for patients with advanced hepatocellular carcinoma (HCC) who received prior treatment with sorafenib (Nexavar).

Pembrolizumab’s accelerated approval for the frontline treatment of patients with cisplatin-ineligible and carboplatin-ineligible locally advanced or metastatic urothelial carcinoma also was supported by a 5 to 3 vote. However, in a 6 to 2 vote, the committee voted against maintaining the accelerated approval of pembrolizumab for the treatment of patients with PD-L1-positive (combined positive score ≥ 1) recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have received 2 or more lines of therapy.

ODAC voted 10 to 1 to uphold the accelerated approval of the PD-L1 inhibitor atezolizumab (Tecentriq) for the frontline treatment of patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma. Additionally, atezolizumab’s accelerated approval for the treatment of patients with metastatic triple negative breast cancer was upheld in a 7 to 2 vote.

Finally, ODAC voted to oppose maintaining the accelerated approval of the PD-1 inhibitor nivolumab (Opdivo) as monotherapy for patients with advanced HCC who received prior treatment with sorafenib by a count of 5 to 4.

FDA Sets Decision Date for Mobocertinib

FDA-approved assay, who have received previous platinum-based chemotherapy. The FDA is expected to decide on the application by October 26, 2021.

The designation is based primarily on findings from a phase 1/2 trial, in which mobocertinib elicited a confirmed objective response rate of 26% (95% CI, 19%-35%) per an independent review committee and a 35% investigator-assessed objective response rate (95% CI, 26%-45%). Additionally, the median progression-free survival was 7.3 months (95% CI, 5.5-9.2) from both independent review committee and investigator assessments.

Findings from 2 cohorts included in the dose-escalation and expansion phase of the trial also demonstrated reductions in target lesion volume. Specifically, in the platinum-pretreated population (n = 114), 82% of patients experienced a reduction from baseline in the sum of target lesion diameter. In the EXCLAIM expansion cohort (n = 96), 80% of patients experienced a reduction.

Mobocertinib, an oral tyrosine kinase inhibitor was previously granted a breakthrough therapy designation by the FDA in April 2020 as a potential treatment for this patient population and is available to patients in the United States through an Expanded Access Program established by Takeda, the agent’s manufacturer (NCT04535557).
NOW APPROVED

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FEWER THAN HALF OF PATIENTS with relapsed/refractory large B-cell lymphoma respond to standard therapies following failure on second-line therapy.1 In clinical studies, CD19-directed chimeric antigen receptor (CAR) T-cell therapies have yielded durable responses with tolerable safety profiles, making such agents an attractive option for patients in the third line and beyond. The approval of liso-
cabtagene maraleucel (liso-cel; Breyanzi) for the treatment of adult patients with relapsed/refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.2

Investigators evaluated liso-cel in the TRANSCEND-NHL-001 trial (NCT02631044). The therapy was administered 2 to 7 days following completion of lymphodepleting chemotherapy, which consisted of fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² daily concurrently for 3 days. Results showed that the overall response rate (ORR) in 192 evaluable patients was 73% (95% CI, 67%-80%), with 54% (95% CI, 47%-61%) of patients experiencing a complete response and 19% (95% CI, 14%-26%) having a partial response. The median duration of response was 16.7 months (95% CI, 5.3-not reached).3

In an interview with OncologyLive®, Amitkumar Mehta, MD, assistant professor in the Division of Hematology and Oncology at the University of Alabama at Birmingham (UAB), director of the UAB Lymphoma Working Group, and codirector of the Bone Marrow Transplant-Immune Effector Cell Therapies Program at the O’Neal Comprehensive Cancer Center, discussed the safety profile of liso-cel and how it is advancing the relapsed/refractory large B-cell lymphoma treatment paradigm.

**Q** What was noteworthy about the efficacy data in the TRANSCEND-NHL-001 trial?

TRANSCEND-NHL-001 was a [study of an] autologous CAR T-cell therapy in patients with relapsed/refractory aggressive B-cell lymphomas, including some patients with of the aggressive follicular 3B lymphoma. It has a very broad range of indications in aggressive B-cell lymphomas.

The efficacy was very impressive. This was a phase 1 study that was expanded to enroll more patients. This was a larger study, with a total enrollment of 344 patients, and ultimately, approximately 256 patients were evaluable. The ORR was 73%, and complete response rate was approximately 53%. This is very impressive for [patients with] relapsed/refractory aggressive B-cell lymphoma in this particular indication.

**Q** Please describe the mechanism of action of liscocabtagene maraleucel.

[Liso-cel] is an autologous CAR T-cell therapy [that begins with] plasmaphere-
sis of a patient’s T cells [to] prepare them to fight CD19-containing B cells. Once the cells are collected, they are expanded and transfected with a vector [contain-
ing the anti-CD19 CAR transgene] on the surface of the T cells. The costimulatory domain for this patient population was 4-1BB, and the inherent T-cell activating domain was CD3ζ. It was a unique construct [that] we could personalize for patients with CD19-positive B-cell lymphomas.

**Q** What should clinicians know about liscocabtagene maraleucel in terms of safety?

There are 2 other CAR T-cell therapies approved in this setting—axi-cel [axicabtagene ciloleucel; Yescarta] approved in 2017 and tisa-cel [tisagenlec-
ulece; Kymriah] approved in 2018—so we have something for comparison. With CAR T-cell therapies, cytokine release syndrome and immune effector cell therapy-associated neurotoxicity [ICAN] are very specialized adverse effects. For liscocabtagene maraleucel, very impressively, the [incidence of] cyto-
kine release syndrome was much lower compared with the other 2 products. [Specifically], the all-grade incidence rate was 42% and 2% for grade 3 or higher.

Rates for all-grade ICAN were 30% and 10% for grade 3 or higher.

Other commonly observed adverse effects included cytopenia, neutropenia, anemia, and thrombocytopenia. [Liso-cel] was overall well tolerated in these patients. Knowing how to identify the cytokine release syndrome and ICAN was a learning curve over the past few years, but we now have a team who can identify these adverse effects quickly so that they can be mitigated.

**Q** How does this approval affect the treatment standards for relapsed/refractory large B-cell lymphoma?

If you look at patients with relapsed/refractory large B-cell lymphoma, they have inferior outcomes overall [to subsequent lines of therapy]. With conven-
tional therapy, ORRs are inferior, and we learned this from SCHOLAR-1 data. SCHOLAR-1 was a retrospective analysis [in which investigators] benchmarked approximately a 20% overall response rate, with single-digit complete response rate, and an overall survival of just 6 months.4

If you compare these data with any of the [newer] CAR T-cell therapies, we have definitely moved the science forward. With liscocabtagene maraleucel, the most important [observation] was that it was well-tolerated and the toxicity rates were far lower [compared with other CAR T-cell products], and it had significantly higher, or at least comparable, response rates. Overall, this is a very important treatment and approval.

Another part I want to highlight is that approximately half of the patients remained in remission at 1 year, so this therapy could be potentially curative in this patient population [for which] there was no cure available.

**Q** What does the future hold for liscocabtagene maraleucel?

One of the most important next steps is outpatient administration in this patient population. Most CAR T-cell therapies are done inpatient, and with the ongoing pandemic, it’s a challenge for these patients to [be admitted for treat-
ment, but] they will sometimes get very ill because of the adverse effects. If a patient [experiences manageable] adverse effects, the therapy could be poten-
tially be rolled out on an outpatient basis. This will expand the access to other patients.

For a full list of references, see the article at OncLive.com.
**PIVOTAL CLINICAL TRIAL**

TRANSCEND-NHL-001 (NCT02631044) was a single-arm, multicenter trial that evaluated lisocabtagene maraleucel, preceded by lymphodepleting chemotherapy, in adults with relapsed or refractory large B-cell non-Hodgkin lymphoma after at least 2 previous lines of therapy.

**BASELINE PATIENT CHARACTERISTICS**

**Median age (years, range)**

- 63 (18-86)
- n = 269

**Disease histology (%)**

- DLBCL, not otherwise specified: 51%
- DLBCL transformed from indolent lymphomas: 22%
- High-grade B-cell lymphoma with gene rearrangements in MYC and either BCL2, BCL6, or both: 29%
- Transformed from primary mediastinal lymphoma: 7%
- Follicular lymphoma grade 3B: 6%
- Transformed from other indolent non-Hodgkin lymphoma subtypes: 1%

**ECOG performance status at screening (%)**

- 0: 41%
- 1: 58%
- 2: 1%

**Prior therapeutic history (%)**

- 67% Received previous HSCT
- 44% Never achieved CR with previous therapy
- 35% Received bridging therapy
- 29% Chemotherapy refractory

**COMMONLY REPORTED ADVERSE EFFECTS IN TRANSCEND-NHL-001 TRIAL SAFETY POPULATION**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Lisocabtagene maraleucel (n = 268)</th>
<th>All grade</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>48%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>46%</td>
<td>4.1%</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>37%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>32%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>30%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Infections (pathogen unspecified)</td>
<td>29%</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCES**

Ide-Cel Proves Highly Effective in Relapsed/Refractory Myeloma

by KYLE DOHERTY

If you look at the number of patients getting CR, at the target dose, it was close to 40% of patients. Within the CR patients, 79% [reached] MRD negativity, so it was quite a deep response. That is why we are so excited, and this is true for all CAR T cells, this is just the beginning. If you look at the standard survival outcomes, the PFS [progression-free survival] overall was 8.8 months. However, patients who got the target dose were close to 12 months and patients with an sCR had a PFS around 20 months. [Overall survival] was 19.4 months, but this is a little bit premature. We will know the real number with a longer follow-up.

**What were some of the important findings in terms of safety?**

Regarding toxicity, almost every [patient] gets cytokine release syndrome [CRS], but it has been grade 1 or 2. At the target dose, approximately 96% of patients got it. Around 4% to 5% of patients had grade 3. For this product, the time to CRS is 1 day, so it’s very quick and very predictable. It lasts anywhere from 3 to 5 days in most of the patients. Neurotoxicity was 18%, so not a very high number. It’s usually grade 1 or 2; only 3% of patients had grade 3 neurotoxicity.

The other adverse effect we are keeping in mind is cytopenia. I think it’s mainly because of lymphodepletion, not because of the CAR T [therapy], but grade 3 cytopenia occurred in 89% of the patients. The bottom line of this study is that ide-cel provides deep responses, durable responses, and we have a really important and effective option available in these triple-class refractory patients.

**Can you expand on the unique advantages this therapy affords patients?**

There are 2 parts to this point. One is that it is a one-time treatment, number 2 is that there is no maintenance. In myeloma, except for this treatment, there is no treatment where we don’t give maintenance. Even after transplant, there is an indefinite maintenance. The quality of life is great and if you added maintenance or something else these numbers could even improve.

Patients are going without any treatment for a long duration and that’s very exciting for the patients; they’re really enthused that they are living a normal life.

**What are the next steps for ide-cel or CAR T-cell therapy in general in myeloma?**

One future advance could be using it at an earlier stage. We have tried using it in the 2-out, 9th-inning setting, and we are getting wonderful responses. We are now leading studies in the second-line and in some cases frontline treatment. [We’re also looking at] new versions of CAR T-cell therapy; [those with] secondary targets that are under investigation and will be important. [Finally, we’re asking] how do we maintain [response]? For example, [can we use] some immune-directed maintenance treatment that keeps it going and functioning? Another [area we are exploring] is the composition of the CAR T cells themselves. Can we enrich for CD4, CD8, or some other types?

**REFERENCE**
**PIVOTAL CLINICAL TRIAL**

KarMMa (NCT03361748) was phase 2, single-arm, open label, multicenter trial that evaluated efficacy and safety of idecabtagene vicileucel in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Median number of prior lines of therapy</th>
<th>Median time since initial diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 (33-78)</td>
<td>6 (range, 3-16)</td>
<td>5.9 months (range, 1.0-17.9)</td>
</tr>
</tbody>
</table>

**EFFICACY RESULTS IN THE KarMMa TRIAL**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Idecabtagene vicileucel (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>72% (62%-81%)</td>
</tr>
<tr>
<td>sCR (95% CI)</td>
<td>28% (19%-38%)</td>
</tr>
<tr>
<td>VGPR (95% CI)</td>
<td>25% (17%-35%)</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>19% (12%-28%)</td>
</tr>
<tr>
<td>MRD-negativity rate* in all treated patients (95% CI)</td>
<td>21% (13%-30%)</td>
</tr>
<tr>
<td>MRD-negativity rate* in patients achieving CR or sCR status (n = 28) (95% CI)</td>
<td>75% (55%-89%)</td>
</tr>
<tr>
<td>Median DOR for PR or better, months (n = 72) (95% CI)</td>
<td>11.0 (10.3-11.4)</td>
</tr>
<tr>
<td>Median DOR* for sCR, months (n = 28) (95% CI)</td>
<td>19.0 (11.4-NE)</td>
</tr>
</tbody>
</table>

**COMMONLY REPORTED ADVERSE EFFECTS IN KarMMa TRIAL**

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Idecabtagene vicileucel (n = 127)</th>
<th>All grades</th>
<th>Grade ≥ 3</th>
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</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
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<tr>
<td>Infections (pathogen unspecified)</td>
<td>51%</td>
<td>15%</td>
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</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>45%</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45%</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>41%</td>
<td>0.8%</td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCE**

INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION

HEMORRHAGE

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.

- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.

- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Please see Important Safety Information and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
“I’m in this for as long as I can be.”

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Adding CYRAMZA to paclitaxel nearly doubles the response vs paclitaxel alone

<table>
<thead>
<tr>
<th>ORR (Complete and Partial Response): Supportive Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAINBOW ORR: percent of patients (95% CI)</td>
</tr>
<tr>
<td>CYRAMZA + paclitaxel</td>
</tr>
<tr>
<td>CYRAMZA + paclitaxel</td>
</tr>
<tr>
<td>Placebo + paclitaxel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + paclitaxel</td>
</tr>
</tbody>
</table>

ORR DOES NOT INCLUDE STABLE DISEASE

- Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
- 2 complete response in CYRAMZA-treated patients and 1 complete response in the placebo-treated patients

CYRAMZA plus paclitaxel significantly extended OS and PFS

<table>
<thead>
<tr>
<th>Overall Survival: Major Outcome Measure Median-Months (95% CI)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + paclitaxel</td>
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</tbody>
</table>

STUDY DESIGN: The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle.1,3

- The percentage of deaths at the time of analysis was 78% [256 patients] and 78% [260 patients] in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively
- The percentage of events at the time of analysis was 85% [279 patients] and 88% [296 patients] in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively
- 56 of 279 events in CYRAMZA-treated patients and 55 of 296 events in placebo-treated patients were deaths

PFS: Supportive Outcome Measure Median-Months (95% CI)

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel</th>
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<td>Placebo + paclitaxel</td>
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SELECT IMPORTANT SAFETY INFORMATION

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

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

Please see Important Safety Information on next page and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%, Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Gastrointestinal Perforations

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

Impaired Wound Healing

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

Arterial Thromboembolic Events (ATEs)

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

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. In 1116 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-16%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRR)

- IRR, including severe and life threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR include rigor/hypothermia, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Worsening of Pre-existing Hepatic Impairment

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Proteinuria Including Nephrotic Syndrome

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

Thyroid Dysfunction

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

Embryo-Fetal Toxicity

- CYRAMZA can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

Lactation

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

Adverse Reactions

REGARD:

- The most common adverse reactions (All Grades) observed in single agent CYRAMZA-treated gastric cancer patients at a rate of ≥5% and ≥2% higher than placebo were hypertension (16% vs 8%), diarrhea (14% vs 9%), headache (9% vs 3%), and hyponatremia (6% vs 2%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.6%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were: neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 5% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

RAINBOW:

- The most common adverse reactions (All Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia (57% vs 44%), neutropenia (54% vs 31%), diarrhea (32% vs 29%), epistaxis (31% vs 7%), hypertension (25% vs 6%), peripheral edema (25% vs 14%), stomatitis (26% vs 7%), proteinuria (17% vs 6%), thrombocytopenia (13% vs 6%), hyposalbuminemia (11% vs 5%), and gastrointestinal hemorrhage events (10% vs 6%).
- The most common serious adverse reactions with CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%). 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (5%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

Please see Brief Summary of Prescribing Information for CYRAMZA on next page.
WARNINGS AND PRECAUTIONS

Hemorrhage
CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade 3 hemorrhagic events. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade Gastrointestinal Perforations
CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade 3-5 gastrointestinal perforations ranged from <1-2%. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway, CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds. Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events
Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have occurred across clinical trials. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE ranged from 1-3%. Grade 3-5 ATE incidence was <1-2%. Permanently discontinue CYRAMZA in patients who experience an ATE.

Hypertension
An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies, excluding RELAX in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 hours or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Realted Reactions
Infusion-related reactions (IRR), including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRR included rigor/myalgia, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypotension, and paresthesia. In severe cases, symptoms included bronchospasm, suprapyramidal tachycardia, and hypotension. Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1-9%. Grade 3-5 IRR incidence was <1%. Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Worsening of Pre-existing Hepatic Impairment
Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration. Based on safety data from RELAX-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepato-renal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome
Posterior Reversible Encephalopathy Syndrome (PRES) (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in ~0.1% of 2137 patients enrolled in six clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. Confirm the diagnosis of PRES with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome
Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade 3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is 2+ or greater, perform a 24-hour urine collection for protein measurement. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction
Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%. There were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

Embryo-Fetal Toxicity
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflects exposure to CYRAMZA in 2137 patients from six studies: REGARD, RAINBOW, RAISE, REVEL, REACH-2, and RELAY.
Cyramza® (ramucirumab) injection, for intravenous use

Immunogenicity
As with all therapeutic proteins, there is the 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 handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

In clinical trials, 86/2890 (3%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of CYRAMZA. Because such 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: Thrombotic microangiopathy
- Neoplasms benign, malignant and unspecified: Hemangiomma
- Respiratory, thoracic, and mediastinal: Dysphonia
- Vascular: Arterial (including aortic) aneurysms, dissections, and rupture

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman. There are no available data on CYRAMZA use in pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise a pregnant woman of the potential risk to a fetus.

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

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

Lactation

Risk Summary
There is no information on the presence of ramucirumab in human milk or its effects on the breastfed child or on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating.

Contraception
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

Infertility

Females
Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use

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

Juvenile Animal Toxicity Data
In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use

Of the 563 CYRAMZA-treated patients in REGARD and RAINBOW, 205 (36%) were 65 and over, while 84 (7%) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Of the 221 patients who received CYZAMZA with erlotinib in RELAY, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Overall, no clinically meaningful differences in effectiveness were observed between these patients and younger patients. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 8%).

Of the 1253 patients in REVEL, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who tested positive for treatment-emergent anti-ramucirumab antibodies, 215 (34%) were 65 and over, while 14 (2%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger patients. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 8%).

Of the 827 patients who received CYRAMZA with docetaxel in REVEL, 237 (38%) were 65 and over, while 64 (7%) were 75 and over. In an exploratory subgroup analysis of REVEL, the hazard ratios for overall survival in patients less than 65 years old was 0.74 (95% CI 0.62, 0.87) and in patients 65 years and over was 1.10 (95% CI 0.89, 1.36).

Of the 529 patients who received CYRAMZA with FOLFIRI in RAISE, 209 (40%) were 65 and over, and 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger patients. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with FOLFIRI and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 8%).

Additional information can be found at www.cyramza.com
Biomarkers Help Predict the Role of Chemotherapy in Biologic Aging

by HYMAN B. MUSS, MD; AND ANDREW B. SMITHERMAN, MD, MSc

BIOLOGIC AGING IS A complex process. There are several theories on why and how we age, and it is probable that none of them account for all the aspects. We are constantly exposed to both internal and external stimuli that, over time, facilitate the aging process. These stimuli include ionizing radiation, ultraviolet light, diet, exercise, oxidative stresses, and perhaps, worst of all, smoking.

All of these can trigger intracellular processes, including DNA methylation, or epigenetic change, telomere shortening and damage, DNA damage, and mitochondrial dysfunction. These factors accelerate cellular senescence—what is thought to be the critical factor in aging and has been shown to increase with age.1,2

Cellular senescence is a condition in which a cell has lost the ability to proliferate, and senescent cells increase in almost all organs and tissues as we age. Over time, these changes ultimately lead to the development of significant comorbidities and the cumulative functional deficits we acquire during aging. However, senescent cells are metabolically active and can produce cytokines and inflammatory proteins—the senescence-associated secretory phenotype—further accelerating aging and promoting malignancy. FIGURE 1 illustrates the effect of age and insults on senescence.

Accumulation of senescent cells is implicated as a cause of tissue reprogramming, osteoporosis, glaucoma, neurodegeneration, type 2 diabetes, changes in the microbiome, immune system dysfunction, dysfunctional tissue repair and fibrosis, and cancer.3 Recent data have shown the potential role of chemotherapy and radiation therapy in accelerating aging. Nowhere is chemotherapy’s effect in accelerating aging more apparent than in children and adolescents treated successfully for childhood malignancy.4 In these patients, by the time they reach 35 years, approximately 30% have the clinical phenotype of a person aged 65 years, as evidenced by dramatic increases in cardiac disease and new second malignancies.

At the University of North Carolina Lineberger Comprehensive Cancer Center, we have focused on the effects of chemotherapy and accelerated aging in cancer. To date, we have studied the effects of chemotherapy on childhood cancer, early breast cancer, and bone marrow transplantation. Our research has explored the role of p16INK4a expression, a robust marker of biologic aging, following on the work of Norman E. “Ned” Sharpless, MD, director of the National Cancer Institute. p16INK4a encodes for a protein that blocks cyclin-dependent kinase, analogous to the cyclin-dependent kinase inhibitors now used in breast cancer, including palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio), that prevent cells from entering the cell cycle.5 This leads to cellular senescence. In murine models, aging is associated with dramatic changes in p16INK4a expression in almost all organs over the animal’s lifespan.6 In human studies, p16INK4a expression is measured in T lymphocytes using a reverse transcription-polymerase chain reaction as a surrogate for aging in other tissues. Studies of p16INK4a expression using other immunohistochemistry methods suggest changes in T cells represent mirror changes in other tissue, and further research in this area is underway.

CREATING A ROADMAP FOR P16INK4A

The change in p16INK4a with aging is not linear, and after 60 years, it appears to plateau for unclear reasons.7 It is possible that those older persons who would have had high levels of p16INK4a expression have already died of age-related illness such as cardiovascular disease, and current studies are addressing this issue.

The large dynamic range of p16INK4a expression—approximately 10-fold over the human lifespan—makes it an ideal biomarker for study. In healthy children and adolescents, p16INK4a expression is low to undetectable, with high levels appearing in older persons. FIGURE 2 shows the effect of age on p16INK4a expression in 594 patients. These data give p16INK4a expression the potential to be an accurate predictor of cell senescence in an individual patient.

For example, if one hypothesizes that senescent cells are less likely to replicate to ameliorate the adverse effects of chemotherapy (ie, myelosuppression or mucositis), then investigators might be able to accurately predict between 2 patients of the same age—one with high p16INK4a expression and one with low—that the patient with higher expression would have less cellular reserve and be more vulnerable to adverse effects. Studies are underway to determine if p16INK4a expression measured before treatment will prove to be a predictive marker of toxicity for currently used adjuvant chemotherapy regimens.

Investigators have examined several hundred patients with early breast cancer and a smaller number with childhood cancer and after bone marrow transplantation, and they have found that most chemotherapy regimens cause rapid and sustained increases in p16INK4a expression.
Changes are seen shortly and dramatically after beginning chemotherapy, persist over time, and are irreversible. In adolescents and young adults treated with chemotherapy, significant increases in p16 INK4a expression were associated with frailty and represented a 35-year acceleration in age among frail young adult cancer survivors. These data mimic what has been clinically noted in large studies of adults who had childhood cancer: Approximately one-third of young adults and childhood cancer survivors aged 35 years have a disease phenotype of a person aged 65 years. Our group has also found that p16 INK4a expression rose dramatically during chemotherapy and persisted during follow-up. Of note, docetaxel/cyclophosphamide regimens were associated with only 11 years of aging, and we found no evidence that anti-HER2 therapy affected p16 INK4a expression. In these studies, accelerated aging due to chemotherapy represents estimates based on the trajectory of p16 INK4a expression in normal patients over their lifespan. We are uncertain of the long-term implications of these changes. In our breast cancer studies, baseline p16 INK4a expression was also associated with fatigue. In a recent unpublished analysis (Mitin N, et al), the difference between a patient’s baseline p16 INK4a expression and a normal value for a patient of the same age—the p16 gap—was highly predictive of chemotherapy-induced peripheral neuropathy with taxane chemotherapy. We also found that baseline p16 INK4a expression is a significant predictor of a p16 change, independent of age or chemotherapy type, with those patients having lower baseline p16 INK4a expression being more likely to have greater changes with any chemotherapy regimen. The reasons for this are unclear, but patients of similar age with higher p16 INK4a expression at baseline may have a greater number of senescent cells indicative of less cellular reserve and less ability to overcome tissue and organ damage. Not all chemotherapeutic agents—for example, taxanes used as a single agent—may be associated with accelerated aging. More detailed studies of patients treated with different agents, including immunotherapeutic and other biologic therapies, and for different types of cancer are needed.

**THE FUTURE OF P16 INK4A**

The long-term implications of changes in p16 INK4a expression with chemotherapy are unknown, but our data suggest that higher levels may be indicators of frailty, a syndrome associate with increased comorbidity, poor quality of life, and shortened survival. p16 INK4a expression has been associated with other diseases of aging, including cardiovascular disease, osteoporosis, and other common illnesses, and our chemotherapy-treated patients with accelerated aging may experience major problems 10 to 20 years after treatment, similar to young adults with cancer, and at a time when they are not likely to be followed by their oncologists.

However, these concerns should not mitigate the use of what has proven to be markedly effective treatment regimens that have dramatically improved overall survival in childhood cancer and breast cancer. It is...
too early to speculate, especially in breast cancer, whether nonanthracycline regimens with similar effectiveness to anthracyclines may be worth considering for patients with long life expectancy. The use of biomarkers in aging research, “geroscience,” is an exciting area of exploration, and p16\(^{INK4a}\) expression is just one of the markers currently being studied.\(^{12}\) The implications of accelerated aging are being studied in other scenarios, and a broad range of studies are exploring interventions to ameliorate biological changes suggesting accelerated aging.

An excellent review of these issues and potential interventions is available\(^{13}\) and describes studies of exercise, diet and nutrition strategies, and senolytics. Learning about the effects of cancer treatment on aging is of major importance, as the clinical scenario of cancer is dominated by older adults who already may have a substantial comorbid illness at the time of diagnosis that might be accelerated by treatment. In children and young adults with cancer, learning how to assess and, in the future, intervene to prevent treatment-related accelerated aging is also a major need. ■

**REFERENCES**


COVID-19
Accommodations May Endure Long After the Pandemic

by KYLE DOHERTY

THE WIDE-RANGING EFFECTS OF the COVID-19 pandemic has required changes to the tried and true methods of patient care. New protocols including video visits and universal masking have been implemented and adjusted as the ramifications of the pandemic have continued to evolve. While some of these adaptations may prove to be temporary, others appear poised to stay long after life returns to something resembling normal.

OncLive® spoke with opinion leaders from a variety of backgrounds in the oncology space to get a glimpse into the future of what approaches adopted during COVID-19 may persist in oncology after the pandemic ends.

BREAST CANCER
Adam M. Brufsky, MD, PhD
University of Pittsburgh Medical Center

Some of the things we adapted into practice will remain after we move back to normal practice including the use of telehealth visits and more of a medical visit at home, where patients can check in and not have a formal visit. Another one is the emphasis on more oral or subcutaneous therapies that can be delivered outside the clinic in the hospital. We need to develop methods to monitor and ensure that patients are getting proper therapy remotely. I think that is going to become a big trend.

I think this is also really going to help patients in rural communities. One of the problems of living in a rural community and receiving a serious diagnosis, such as metastatic breast cancer, for example, is that [care centers are often] far and the patient may have to travel. I care for a lot of patients who travel 3, 4, 5 hours to see me and I think some of the remote strategies that have been developed during the pandemic could really be used for the benefit of patients such as those. I’m looking forward to exploring those sorts of innovations.

SARCOMA
Brian Van Tine, MD, PhD
Siteman Cancer Center

I think that tumor boards will now be virtual. Zoom is not going anywhere anytime soon. I think our approach to medicine [will continue to expand] beyond just in the state that we work. I think that’s had an effect, but it’s a little bit harder with oncology in terms of treating. [However,] patients now may not need to fly to New York to get a second opinion.

I think that has an effect on the patients’ ability to get access. It may have gotten a little bit easier; however, in terms of treatment decisions, patients still need to get somewhere they can receive care. We’ve also gained the ability to give scan results by telephone, which we could never do before, and it’s improved the efficiency of my clinic. Additionally, patients are no longer allowed to wait in the waiting room anymore, so it seems like waiting times have fallen dramatically.

I think there has been a lot of good in terms of process improvement.

HEAD, NECK, LUNG CANCERS
Everett E. Vokes, MD
University of Chicago Medicine and Biological Sciences

I would hope that telemedicine will remain. It’s complicated by laws and licensing arrangements that I am certainly not an expert on—particularly, in terms of what is allowed across states. But [I’d like to see] the general principle of seeing a patient not always in person, certainly sometimes, maybe most of the time, but not always in person, for follow-up visits. To move that into the future and to continue that is going to be mandatory. This cannot go away; it serves patients’ needs to have this available.

LUNG CANCER
Edward B. Garon, MD
Ronald Reagan UCLA Medical Center

I think that although most visits will remain in person once concerns related to COVID-19 decrease, there are likely to be some visits that will continue to be conducted by video. One hope is that some unhelpful constraints of clinical trials that increase inconvenience to patients and limit the number of practices that can offer clinical research [will be eased] and could inform future trials.
There are some good things. I will say that the telehealth I think of as a relatively good thing and I don’t think telehealth would have happened in medicine to this scale and extent without COVID-19. One of the really good things is that with telemedicine everything—including reimbursements, physician/provider acceptance, and patient acceptance, as well as comfort levels [with the technology]—has been overcome because of COVID-19. Now, telemedicine is part of our culture just like this conversation is part of our culture.

I think another good thing is that we have so many patients who travel from a distance, so many patients who don’t have access to support or caregivers to travel with and take them [to their appointments]. This includes many folks whose children or spouses once would have to take time off work and miss time in order to accompany them to visits on a regular basis. All of that is now really alleviated by telemedicine. I’m not saying that we will or should practice exclusively in telemedicine, I think that’s a little dangerous; however, what we’ve found is that a lot of what we do in medicine can be done via the computer or the phone.

We’ve learned to trust local labs and trust a lot of the information that we would we have adapted these approaches. I have many patients who I believe are more satisfied with their care now because they don’t have to come to clinic, they don’t have to wait for hours to see the physician. Another advantage is that I have my full attention to the patient [in person] as they speak and move gives you a lot of information and [in person visits are needed, especially] if you’re doing scans as well.

The video visits will definitely continue, as well as the pattern of less frequent scheduling [for patient appointments]. Additionally, less frequent dosing of some medications will continue. I’m hopeful that some of the changes to clinical trials will also persist, including drug shipments that can be sent to patients without them having to come in from quite a distance in some cases.

Learning to lead by example I think is a very important lesson [we can take away from this pandemic] and as health care providers we are in the center of this where even though we were in a crisis, society is looking for some guidance on what to do and how to behave. Many of us stepped up to the plate and led by example. I think the pandemic also taught us to be more flexible in terms of accepting the reality and the challenges of working with the best tools you have to survive the current situation. Hopefully, this made us stronger, and I believe it did.

Hopefully, what I think will carry on is preparation for the next challenge that may be of similar nature but may be different. Being able to mobilize and rely on the team effort, to be flexible and adapt to the situation is very important.

Certainly technology has been very important in allowing us to survive and adapt, so continuing to rely on this technology will be something that we will carry forward. We’ve all seen the advantages technology [affords us] that we may not have been aware of in the pre-COVID-19 era. Many of us continue to practice health care on a day-to-day basis in the same old way, even though the world has been moving at a much faster pace in terms of adapting these technological advances.

Health care is a very complex system and we don’t necessarily accept big changes, especially when approaching familiar situations where we are already stressed with the volume of work we have because certain aspects of what we do may be easier [without change]. If you move just one part of the system, many of the other parts that are intricately linked will be affected. But we were forced to make changes and we were forced to adapt to relying on more electronic or virtual types of activity with COVID-19.

The good part of this is that we are in a position to improve patient care because we have adapted these approaches. I have many patients who I believe are more satisfied with their care now because they don’t have to come to clinic, they don’t have to wait for hours to see the physician. Another advantage is that I have my full attention to the patient during virtual visits, I’m not distracted because I am in an office looking at the patient face to face and at the same time accessing their records. It’s important to understand that this may be a slippery slope and individuals may think that because of these changes health care may be becoming so easy or so uncomplicated.

I want to stress that I have a hard time seeing health care moving completely to a virtual system where you don’t need to be linked to a specific hospital or specific physician. That may apply if you need an antibiotic, it may apply for minor things if you need some advice quickly about something, including some situations with cancer. But I do not think [it will overtake care] in terms of the complex management of chronic health care problems such as cardiac disease or cancer. Those remain very much dependent on a very thorough evaluation, which cannot be done in a virtual setting.

What I have noticed is that, even though there are some patients who gain by doing the virtual process, other patients may lose. You’re dealing with a situation that is so complex; dealing with it on a computer screen is a disservice to them. You need to coordinate with the health care team, you need to have your nurses, your schedulers, other colleagues close to you. The more we learn how to funnel each type of patient to a particular method of evaluation will serve us in the future.
Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Important Safety Information

Warnings and Precautions

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

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Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS
The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

* Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS
CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS
Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib)

**Cardiac Arrhythmias and Cardiac Failure:**

Cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmias and cardiac failure. At baseline and then periodically, monitor patients clinically for cardiac adverse reactions [see Adverse Reactions].

IMBRUVICA in clinical trials. These events have occurred particularly in 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without antplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antithrombotic therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antithrombotic therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antithrombotic therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding [see Clinical Studies (14) in Full Prescribing Information].

**Hypertension** occurred in 19% of 1,476 patients who received IMBRUVICA. Major hemorrhage: Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage (including subdural hematoma), gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively.

**CONTRAINDICATIONS**

- None

**WARNINGS AND PRECAUTIONS**

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Monitor complete blood counts monthly.

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Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

**Second Primary Malignancies:** Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

**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.
One patient death due to histiocytic sarcoma.

5.3 months in RESONATE in patients with previously treated CLL/SLL.

Duration of 8.6 months and exposure to ofatumumab with a median of 17.4 months.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

1 Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

The median exposure to chlorambucil was 7.1 months below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 17.4 months.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>18</td>
<td>2</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>14</td>
<td>0</td>
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<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
<td>0</td>
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<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>20</td>
<td>0</td>
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<tr>
<td></td>
<td>Headache</td>
<td>18</td>
<td>2</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td>Second malignancies</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Percent of Patients (N=51)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>13</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
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</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>10</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>11</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Contusion</td>
<td>11</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Percent of Patients (N=195)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
<td>0</td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
</tr>
</tbody>
</table>
**Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA® Treated Arm in Patients with CLL/SLL in RESONATE-2**

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA® (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%) Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Rash*</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Skin infection</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2**

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA® (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%) Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 7: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA® Arm in Patients with CLL/SLL in HELIOS**

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + BR (N=267)</th>
<th>Placebo + BR (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%) Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA® arm.

**Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA® Arm in Patients with CLL/SLL in iLLUMINATE**

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%) Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Rash*</td>
<td>32</td>
<td>3</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA® arm.

* Includes multiple ADR terms

† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA® arm

‡ Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA® arm

<1 used for frequency above 0 and below 0.5%

* Includes multiple ADR terms
IMBRUVICA® (ibrutinib)

Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in ILLUMINATE (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes one event with a fatal outcome.

E1912: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.

Table 9: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912 (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 10: Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)

<table>
<thead>
<tr>
<th></th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematologic abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>AST increased</td>
<td>25</td>
<td>3</td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria.
IMBRUVICA® (ibrutinib)

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid concomitant use of other strong CYP3A inhibitors. Intermitt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities (see Data). Advise pregnant women of the potential risk to a fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the United States general population is approximately 2-4% and 15-20%, respectively. Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MZL) and 20 times the exposure in patients with CLL/SLL or Waldenström’s Macroglobulinemia (WM) administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily. Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Contraception: There is no information regarding the presence of ibrutinib 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 in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose.

Females and Males of Reproductive Potential: Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating IMBRUVICA.

Contraception: Females: IMBRUVICA can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose.

Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 0.4% versus 1.8% and for Grade 3 or greater was 4.0% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of cardiac failure of any grade was 1.7% versus 0.5% and for Grade 3 or greater was 1.2% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) of any grade was 0.4% and Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea in IMBRUVICA-treated patients occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,605 of these patients, the median time to first onset was 3 days (range, 0 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 58) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3). Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively.

The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analyzed. The median treatment duration was 51 months (range, 0 to 98 months) for CLL/SLL, 11 months (range, 0 to 97 months) for MCL, and 47 months (range, 0 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall rate was 1.2%.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of IMBRUVICA. 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.

- Cardiac events: atrial fibrillation and atrial flutter
- Gastrointestinal: diarrhea, decreased appetite
- Hematologic: anemia, thrombocytopenia
- Hepatic: elevated AST, elevated bilirubin
- Metabolic and nutrition disorders: diabetes mellitus
- Neurological: peripheral neuropathy
- Pulmonary: pneumonia
- Skin: rash
- Thyroid: hypothyroidism
- Vision: decreased vision, blurred vision
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy
- Other: postural hypotension
Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

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

- Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].
- Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].
- Cardiac arrhythmias and cardiac failure: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema [see Warnings and Precautions].
- Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].
- Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].
- Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].
- Embryo-fetal toxicity: Advise 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, Use in Specific Populations].

Advising females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations].

Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations, Nonclinical Toxicology (13.1) in Full Prescribing Information].

Lactation: Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose [see Use in Specific Populations].

Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].

Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].

Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

Active ingredient made in China.
ROY S. HERBST, MD, PhD, was inspired to become an oncologist during his first week as an MD/PhD candidate at Cornell University and The Rockefeller University, thanks in part to Ralph L. Nachman, MD, longtime chair of Weill Department of Medicine at Weill Cornell Medical College.

Herbst can remember going on rounds with Nachman as a young physician, seeing patients with Hodgkin lymphoma and reviewing the micrographs at teaching rounds. He knew then he was interested in cancer. Treating patients with cancer became personal when Herbst's mother developed an early-stage breast cancer during his second year of medical school. She would send a giant packet of pathology slides from her home in Florida to him in New York and he would review them with experts in breast pathology at Cornell and Memorial Sloan Kettering Cancer Center (MSK). At the time, Herbst was working in the laboratory of James E. Darnell Jr, MD, a pioneer in the study of RNA processing and cytokine signaling. The young physician found that oncology fit his research and clinical interests. Plus, he felt good helping his mother navigate through her cancer diagnosis and treatment, a joy he now experiences with his patients.

Herbst enjoyed working in hematology and initially considered specializing in leukemia and lymphoma, but that was a crowded field. He also considered specializing in breast or gastrointestinal cancers, but those fields also didn’t leave much room for an ambitious young investigator.

Arthur T. Skarin, MD, his clinical mentor at MSK, recommended Herbst to the late, legendary Emil “Tom” Frei III, MD, former director and physician-in-chief at Dana-Farber Cancer Institute, and they both encouraged Herbst to pursue lung cancer. It was the mid-1990s and decades had passed since the last major advance in the field. Frei told the younger physician there was no place to go but up in lung cancer and that he had the opportunity to make a significant difference.

Herbst saw an opportunity to bring science from the laboratory to the clinic and began seeing patients under the direction of the late thoracic surgeon David J. Sugarbaker, MD. His mentor and fellowship director Robert J. Mayer, MD, a 2015 Giants of Cancer Care® award winner in the gastrointestinal cancer category and vice president for faculty affairs at Dana-Farber, also gave Herbst’s career a boost. Mayer nominated him for the first class of the newly established clinical investigator training program at the Harvard-MIT Program in Health Sciences and Technology, where Herbst would go on to earn a master’s degree in human clinical investigation.

“There wasn’t much competition for the job in lung cancer back then,” he said. “Now it’s very competitive to work in this field.”

Certainly, Herbst, a pioneer in designing novel clinical trials and developing new therapies, has helped turn the lung cancer treatment landscape into one of the most active in oncology today. Along the way, Herbst has worked at some of the best medical centers in the world, first at Dana-Farber, then at The University of Texas MD Anderson Cancer Center, and now back at his undergraduate alma mater of Yale University. There, he is Ensign Professor of Medicine (medical oncology) and professor of pharmacology, chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital, and associate director for...
translational science at Yale Cancer Center. He also serves as an undergraduate adviser and enjoys working with the trainees and junior physicians.

His friend Thomas J. Lynch Jr, MD, a 2013 Giants of Cancer Care® award winner for lung cancer who is now president and director at Fred Hutchinson Cancer Research Center, formerly served as director of Yale Cancer Center and recruited Herbst back to Yale. Herbst’s wife and daughter are longtime Texans—he is a graduate of The University of Texas and their daughter was born there—so they weren’t thrilled with trading Houston for New Haven, Connecticut. Now, the family is thriving in the Northeast. “They love it here. It’s a good community,” he said. “We live right in the heart of New Haven—the university is a mile and a half away. The Yale Bowl where they play football is 2 blocks away and we often walk over there to see a game or walk the dog. I can even walk to the office on a nice day. We enjoy every aspect of life.”

“SHOVEL-READY” DATA FOR THE CLINIC

As an innovative investigator in the lung cancer arena, Herbst enjoys communicating with his colleagues about emerging treatment strategies and best practices. He has been involved with the International Lung Cancer Congress® (ILCC) since it was founded 22 years ago except for 2005, when he missed the meeting for the birth of his daughter. In 1999, conference founder Chandra P. Belani, MD, invited him to address the inaugural congress.

Several years later, Herbst joined the steering committee for the meeting, which is hosted by Physicians’ Education Resource®, LLC (PER®). He and David R. Gandara, MD, emeritus professor of medicine and director of the Thoracic Oncology Program at UC Davis Comprehensive Cancer Center and the 2017 Giants of Cancer Care® award winner for lung cancer, have cochaired the conference for more than a decade.

This year’s meeting, scheduled for July 29 to 31, will be a hybrid conference that includes both virtual and in-person sessions in Huntington Beach, California. Herbst said he will attend in person “by hook or by crook.”

“I really like the in-person interaction, so I will figure out a way to get there,” he said, adding that will be nice to get away and see some colleagues in person. “I’m vaccinated and ready to go. The idea of reviewing data about lung cancer, discussing cases and having knowledge exchanged between academic and community physicians—I look forward to it every year.”

Herbst is cochairing this year’s meeting with Gandara and Heather A. Wakelee, MD, a professor of medicine at Stanford University Medical Center in Palo Alto, California. They were still working on the agenda when Herbst spoke about the conference in April, but he said the meeting would include sessions on early and metastatic disease, targeted therapy, immune checkpoint inhibitor (ICI) therapy, radiation, surgery, and multimodal therapy. There also will be a series of debates and case discussion panels, which are always a highlight of the meeting.

“We’re very excited this year because we’re going to have an increased number of discussion sections, we’ll be very case focused,” he said. “We’re expecting new adjunct data to be out by the meeting, so we can discuss those data. Dr Wakelee has been involved with that research. In every panel, we’ll have cases with audience questions and response, then we’ll discuss it in a multimodality way.

“I am excited about creative ways to interact with both the in-person and virtual attendees,” Herbst added. “This is certainly the way we will be doing these types of meeting in the future.”

**FIGURE. A Closer Look at Lung-MAP**

Lung-MAP is a master protocol that uses a comprehensive genomic profiling platform that looks at over 200 cancer-related genes for genomic alterations in patients with advanced non–small cell lung cancer. Based on the results of this screening, patients are assigned to a substudy evaluating different investigational treatments.1

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Recent findings from 3 translational medicine studies

- **SWOG S1400 next-generation sequencing data compared with The Cancer Genome Atlas data**
  - Results: Mutually Exclusive Gene Set Analysis (MEGSA) identified 2 nonoverlapping sets of mutually exclusive gene alterations with a false discovery rate (FDR) <15%.
  - **NF2L2, KEAP1,** and **PARP4** (FDR, 4.1%) and **CDKN2A and RB1** (FDR, 13.1%)

- **ctDNA analysis supports role for enrollment in Lung-MAP substudies**
  - Results: 129 patients had paired data for tissue and plasma ctDNA.
  - 52 patients had drivers detected in tissue; of these 43 were also observed in ctDNA, with 9 found in tissue only, for a ctDNA driver sensitivity of 83% (95% CI, 74%-93%).
  - Of the 77 patients with no drivers in tissue, 2 drivers were detected in ctDNA (EGFR exon 20 insertions, MET amplification) for a ctDNA specificity of 97% (95% CI, 91%-100%)

- **High tumor mutational burden (TMB) is associated with improved overall survival (OS) and progression-free survival (PFS) in patients treated with immune checkpoint inhibitors in substudies S1400I (nivolumab plus ipilimumab vs nivolumab) and S1400A (durvalumab)**
  - Results: Higher TMB per 10-unit difference in TMB value was significantly associated with better OS (HR, 0.80; 95% CI, 0.67-0.94; P = .008) and PFS (HR, 0.80; 95% CI, 0.69-0.93; P = .004).
  - PD-L1 expression was not significantly associated with OS or PFS (N = 16; P= .05)

**REFERENCES**

He noted that ILCC faculty members will discuss data presented at meetings hosted by the American Society of Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer (IASLC), and the American Association for Cancer Research (AACR). Specifically, Herbst is looking forward to examining findings for non-small cell lung cancer (NSCLC) from trials including IMpower010 (NCT02486718), Lung-MAP (NCT02154490), and CheckMate 816 (NCT02998528).

The phase 3 IMpower010 study compared atezolizumab (Tecentriq), a PD-L1 inhibitor, with best supportive care (BSC) as adjuvant therapy for patients with stage II to IIIA NSCLC who had received surgery and chemotherapy. The study randomized 1005 patients to up to 16 cycles of atezolizumab vs BSC.1 Atezolizumab demonstrated a statistically significant improvement in disease-free survival, the primary end point of the study, according to Genentech, the company developing the drug.1 Wakelee and colleagues are scheduled to present primary results from the trial during the 2021 ASCO Annual Meeting, which will be held virtually June 4 to 8.2

In Lung-MAP, which began in 2014, investigators have been using an umbrella design to conduct molecular testing on the tumors of patients with NSCLC to match them with targeted therapies. The study, for which Herbst serves as the founding and current PI, has recruited more than 3660 patients who have been treated at 800 centers with novel targeted therapies. The study, for which Herbst serves as the founding and current PI, has recruited more than 3660 patients who have been treated at 800 centers with novel therapies during 13 substudies.3 The protocol represents a milestone for precision medicine not only in trial design but also in the amount of information that has been compiled. “Lung-MAP now has one of the largest collections of data and biospecimens ever gathered for lung cancer,” Herbst, who chairs the study, said in a statement.3

In January, translational discoveries from the study were presented at the virtual 2020 World Conference on Lung Cancer. Findings showed that higher tumor mutational burden was associated with better survival rates and longer disease-free periods; that mutations in a previously undetected set of 3 genes, PARP4, NFE2L2, and KEAP1, may play an important role in driving squamous cell lung cancers; and that analysis of plasma circulating tumor DNA shows high sensitivity and specificity as a screening tool for genomic aberrations.1 At the 2021 AACR Annual Meeting in April, investigators shared data from the phase 3 CheckMate 816 trial testing the combination of nivolumab (Opdivo) plus platinum doublet chemotherapy vs chemotherapy alone as neoadjuvant therapy for patients with resectable stage IB to IIA NSCLC. The addition of nivolumab increased the rate of pathologic complete response (pCR) to 24% compared with 2.2% with chemotherapy alone (odds ratio, 13.94; 99% CI, 3.49-55.75; P < .0001). Among those who subsequently underwent resection, the pCR rate was 30.5% with nivolumab compared with 3.2% for chemotherapy alone.4

Herbst said that, like other meetings organized by PER®, ILCC will focus on delivering information physicians can quickly apply to clinical practice. “Everything about our meeting is practical. We discuss the data, then discuss how to apply them with cases and in patients.” This year, Herbst said, the most pressing clinical questions include: “How do you use adjuvant therapy? Do you use neoadjuvant therapy based on pathologic complete response rate? What combinations are more impactful for immune resistance? How do you define immune resistance? How do you use biomarkers and immune resistance? I think all of that will be very important.”

NEW THERAPIES RESULT IN IMPROVED SURVIVAL

Herbst has been a leader in clinical research for nearly 25 years. When he started his career in 1994, lung cancer was no place for an ambitious, young scientist to focus. The only treatment option for metastatic disease was cytotoxic chemotherapy, which put patients through significant adverse effects with very little benefit. In 2001, the 2-year survival rate was 26% for men with NSCLC and 35% for women. Today, those numbers are 35% and 44%, respectively.5 Since then, multimodality treatments, targeted therapy, and immunotherapy have improved outcomes for patients. Lung cancer-specific mortality declined 3.2% annually for men from 2006 to 2013. From 2013, when the FDA approved the EGFR-directed therapies in the first line, to 2016, mortality declined 6.3% every year. For women, mortality declined by 2.3% from 2006 to 2014 and by 5.9% from 2014 to 2016.5

Herbst modestly jokes that witnessing such drastic improvements in survival just means he’s getting old, but he has played a significant role in pushing lung cancer care forward. He began his research career focusing on developing novel targeted agents for...
the treatment of lung cancer, especially therapies targeting the EGFR and VEGF signaling pathways such as gefitinib (Iressa), erlotinib (Tarceva), axitinib (Inlyta), cetuximab (Erbilux), and bevacizumab (Avastin).

“Some of my most impactful early work was to lead the first phase 1 studies for the use of EGFR inhibitors in lung cancer, understanding their use, their toxicity, their response, bringing those drugs to the clinic, and understanding biomarkers involved in their use. And then, of course, bringing them all the way to phase 3 in untreated patients as adjuvant therapy with a highly positive results,” he said.

Moreover, Herbst has been instrumental in developing ICIs directed at PD-1/PD-L1, including the development of PD-L1 as a prospective biomarker. “[In] the early studies on IO [immuno-oncology] inhibitors, whether it be at atezolizumab or pembrolizumab [Keytruda], we carefully explored PD-L1 as a biomarker, which has turned out to be very important,” Herbst said. “Those are all things that have been successes that I’ve been involved with…developing new combination therapies when possible to do so with biomarker targets.”

Herbst was the lead author for the phase 1 trial investigating the first-generation EGFR tyrosine kinase inhibitor (TKI) gefitinib. He later served as principal investigator (PI) on the phase 3 INTACT 2 trial, the results of which supported FDA approval in May 2003 for gefitinib for treating patients with locally advanced or metastatic NSCLC.

In December 2020, the FDA approved the third-generation EGFR-inhibitor osimertinib (Tagrisso) as adjuvant treatment following tumor resection for patients with resected NSCLC whose tumors harbor EGFR exon 19 deletions or exon 21 L858R mutations. The agency granted approval based on data from the ADAURA trial (NCT02511106).

Herbst was the senior and corresponding author for ADAURA, in which 682 patients with resectable (stage IB-IIIA) NSCLC were assigned to the osimertinib arm (95% CI, 38.8-not estimable [NE]) compared with 19.6 months (95% CI, 16.6-24.5) with placebo (HR, 0.17; 95% CI, 0.12-0.23; P < .0001). In the overall study population, which comprised patients with stage IB to IIIA disease, median DFS was not reached in patients in the osimertinib arm (95% CI, NE-NE) compared with 27.5 months (95% CI, 22.0-35.0) for placebo (HR, 0.20; 95% CI, 0.15-0.27; P < .0001). The 83% improvement in DFS with osimertinib with significantly decreased metastatic disease to the brain was paradigm changing.

A decade before the success of osimertinib, Herbst made his mark on the lung cancer field as a PI of the BATTLE clinical trial, along with his late mentor Waun Ki Hong, MD, the 2018 Giants of Cancer Care® award winner for lung cancer, and other team members from his section of thoracic medical oncology at MD Anderson. BATTLE was the first completed, prospective, biopsy-mandated, biomarker-based, adaptively randomized trial in patients with heavily pretreated lung cancer. The study required tumor profiling with “real-time” biopsies, integrating molecular laboratory findings for identifying patient populations for individualized treatment and representing a substantial step toward personalized lung cancer therapy.

Moving forward, Herbst would like to apply some of the lessons from his targeted therapy studies to immunotherapy. “I really would like to now lead a team to undertake personalized immunotherapy. I’d like to find the right biomarkers,” he said. “We did the BATTLE trial and I’d very much like to do the same thing with immunotherapy—pick
the right markers and the right drugs, truly target immunotherapy in the best way.”

Immunotherapy has long been one of Herbst’s clinical interests as he searches for ways to make care more personalized. He works closely with some of the most prominent leaders in the field, including Lieping Chen, MD, PhD, a 2018 Giants of Cancer Care® award winner in the immuno-oncology category; Scott Gettinger, MD; Mario Sznol, MD; and Harriet M. Kluger, MD.

He and his colleagues at Yale were among the first to understand and describe how the presence of PD-L1 correlated with response in patients receiving atezolizumab. This led to a biomarker-driven first-in-human trial, one of the first to demonstrate in human biopsies the concept of adaptive immunity.12,13

Herbst and his collaborators later showed the value of PD-L1 as a prospective biomarker in the randomized phase 2/3 KEYNOTE-010 trial (NCT01905657), in which investigators examined pembrolizumab in the second line setting for patients with NSCLC. Findings from KEYNOTE-010 and KEYNOTE-024 (NCT02142738) contributed to the FDA approval in 2016 for pembrolizumab, the first approved anti-PD-1 agent, as first-line treatment of patients with NSCLC with high PD-L1 expression.14,15

Immunotherapy has resulted in incredible gains in survival for patients with NSCLC; data from KEYNOTE-024 showed that pembrolizumab doubled median overall survival (OS) compared with chemotherapy (26.3 vs 13.4 months).16 Findings published in 2020 showed that immunotherapy improves survival compared with chemotherapy for patients with metastatic NSCLC regardless of line of treatment.17

Additionally in 2020, Herbst and his colleagues published new data from the phase 3 IMpower110 trial (NCT02409342) demonstrating that patients with high PD-L1 expression who received atezolizumab had a median OS of 20.2 months compared with 13.1 months for those who received chemotherapy (HR, 0.59; P = .01).

The findings led to FDA approval for atezolizumab as first-line therapy for patients with high PD-L1 expression (PD-L1 staining on ≥ 50% of tumor cells or ≥ 10% of tumor-infiltrating immune cells) and with no EGFR or ALK genomic tumor aberrations.18,19

UNMET NEEDS

However, for all the improvements in lung cancer treatment, survival still need to be improved. According to Cancer.net, the overall 5-year survival rate is 21%, 17% for men and 24% for women.20

Long-term results from the KEYNOTE-001 trial (NCT01295827) showed that the 5-year OS rate exceeded 25% among patients with a PD-L1 tumor proportion score of 50% or greater (PD-L1 high) who were treated with pembrolizumab monotherapy. This is a huge improvement over previous treatments but one that still leaves many patients without a survival benefit.21

Moreover, not all patients who are PD-L1 high respond to immunotherapy.22 Of those who do respond, up to 27% of patients with advanced NSCLC exhibit resistance to first-line ICIs with or without chemotherapy and up to 44% develop resistance to ICI monotherapy in the pretreatment setting.23

“We have to look the nonresponders and understand what else is going on, identify what other immune regulatory mechanisms are in play. So we can then target them with precision combination therapies,” Herbst said.

Solving those mysteries, he continued, will require translational research bridging the lab and the clinic to bring the best science to bear on the problem. This will likely involve biopsies, combination studies, more preclinical lab work, and preclinical models.

He’s even more focused on understanding how and why patients initially respond, then become refractory to treatment. Herbst leads the Lung Specialized Programs of Research Excellence (SPORE) in Lung Cancer at Yale Cancer Center that is currently conducting multiple trials, including evaluating approaches to prevent TKI-resistance in EGFR-mutant lung cancer and developing ways to target lung cancer metastasis and drug resistance in the central nervous system. He is also working to bring new targets to the clinic, many of which were discovered in the laboratory of his friend and collaborator Chen. “We’re constantly trying to understand how to treat these tumors. We are uncovering resistance mechanisms. We now know that [EGFR] C797S is a resistance mutation to some other targets, so we’ll hopefully find ways to target that,” Herbst said. “That is what keeps me going, trying to find new combinations, new immunotherapies, and always using biology to promote even better therapy.”
The 22nd Annual International Lung Cancer Congress® will distill the latest data on targeted agents, immunotherapy, surgery, and radiation oncology to provide you with current and practical information on the management of patients with lung cancer. As in previous years, we will also preview novel agents and strategies with the potential to shape the future of lung cancer therapy.

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Messersmith Makes Sense of Novel Approaches on the Rise in GI Malignancies

by COURTNEY MARABELLA

THE PIPELINE OF NEW AGENTS in gastrointestinal (GI) cancers is robust, with the emergence of several antibody-drug conjugates (ADCs), KRAS G12C inhibitors, and novel tyrosine kinase inhibitor (TKI)/immune checkpoint inhibitor combinations, according to Wells Messersmith, MD.

“There are some interesting signals with checkpoint inhibitors and TKIs, but we just do not know who is going to respond,” said Messersmith during a presentation at the 6th Annual School of Gastrointestinal Oncology®. “Most of these [efforts] have at least a biomarker hypothesis and how we find these rare subsets is going to be a challenge for the field.” Messersmith is a professor of medicine and medical oncology, and associate director for translational research at the University of Colorado Cancer Center in Aurora.

The heterogeneity of tumors in GI cancers continues to pose a challenge. As such, understanding how circulating tumor DNA will play into the treatment of patients as RAS inhibitors emerge in the clinic will be an area of interest going forward, Messersmith added.

ADCs have shown promising activity in small subgroups of patients, including those with KRAS G12C-mutated disease; however, disappointing results have thus far limited their use in patients with RAS-mutant disease. At least 3 studies are underway to evaluate approaches in patients with other RAS mutations, Messersmith said.

ANTIBODY-DRUG CONJUGATES

ADCs were first proposed as far back as the 1980s, but it took until the early 2000s for the first one to be approved for use. In 2011, brentuximab vedotin (Adcetris) was approved for patients with Hodgkin lymphoma.

ADCs approved for the treatment of patients with solid tumors include T-DM1 and fam-trastuzumab deruxtecan-nxki (Enhertu) for HER2-positive breast cancer and HER2-positive gastric cancer, enfortumab vedotin-ejfv (Padcev) for locally advanced and metastatic urothelial carcinoma, and sacituzumab govitecan-hziy (Trodelvy) for triple-negative breast cancer.

ADCs are made up of an antibody, which is the target of the antigen, along with a cytotoxic payload. “Several steps have to happen for ADCs [to work effectively],” Messersmith said. “[The ADC] needs to bind to an antigen, it has to get internalized, and then through endosomal and lysosomal biology, which is as of yet not all that understood in terms of the predictors of efficacy, [it will] release the payload. That’s where the magic bullet part of this comes in, where [the ADC] releases the payload at site of tumor. Then the payload does its thing in terms of killing tumor cells. For each of these steps, you can see where you get mechanisms of resistance.”

One of the most important advances in the past decade has been the development of linkers. Having a linker that is strong enough to hold the payload in circulation is critical, but it also must release the cytotoxic payload to the tumor site, Messersmith explained. “It took many, many years to get the right linkers in place to actually accomplish these goals,” he said.

In January 2021, the FDA approved trastuzumab deruxtecan for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a previous
trastuzumab (Herceptin)-based regimen. This ADC consists of an anti-HER2 antibody with a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase 1 inhibitor (TABLE 1-3).

“The inhibitor has actually been a more common payload [to emerge] over the past several years,” Messersmith said.

The regulatory decision was based on data from the phase 2 DESTINY-Gastric01 trial (NCT03329690), which included patients with HER2-expressing advanced gastric or GEJ adenocarcinoma who had received at least 2 prior treatments, including fluoropyrimidine and a platinum agent. Eighty-six percent of patients had received prior treatment with taxanes and 33% had prior treatment with checkpoint inhibitors.

A total of 187 participants were randomized 2:1 to receive either trastuzumab deruxtecan at a dose of 6.4 mg/kg in a 3-week cycle (n = 126) or physician’s choice of either irinotecan or paclitaxel (n = 62).

The median overall survival (OS) for patients treated with trastuzumab deruxtecan was 12.5 months (95% CI, 9.6-14.3) compared with 8.4 months (95% CI, 6.9-10.7) with physician’s choice (HR, 0.59; 95% CI, 0.39-0.88; P = .0097).4

The confirmed objective response rate (ORR) with trastuzumab deruxtecan was 40.5% (95% CI, 31.8%-49.6%), with 7.9% of patients having a complete response (CR) and 32.5% having a partial response (PR). The ORR in patients treated with physician’s choice therapy was 11.3% (95% CI, 4.7%-21.9%) and all responses were PRs.

“In the third-line setting, to have response rates that high is actually pretty impressive,” Messersmith noted. “You can see that 10 patients had a CR, while 41 patients had a PR, and the disease control rate was 85.7%. [The agent] was quite active, so you could see why the FDA would approve it, despite the fairly limited patient numbers.”

Additionally, the median PFS in the investigative and control arms was 5.6 months (95% CI, 4.3-6.9) vs 3.5 months (95% CI, 2.0-4.3), respectively (HR, 0.47; 95% CI, 0.31-0.71).

“[These survival rates] go down gradually; they are not leveling like they do with immunotherapy,” Messersmith said.

“However, [these are still] fairly impressive results when you compare them with [what has been seen with] trifluridine and tipiracil [TAS-102; Lonsurf], regorafenib [Stivarga], or some of these other drugs that we use in the third-line setting for other GI cancers.”

In the phase 2 DESTINY-CRC01 trial (NCT03384940), trastuzumab deruxtecan was examined in patients with unresectable and/or metastatic, HER2-expressing colorectal cancer. The primary end point for this trial was ORR by independent central review in cohort A. Notably, patients who had received prior HER2-targeted treatment were permitted to participate.

The ORR was 45.3% (95% CI, 31.6%-59.6%), and tumor shrinkage over time was well sustained. Specifically, 1.9% of patients had a CR and 43.4% had a PR. The median PFS was 6.9 months (95% CI, 4.1-not evaluable) and the median OS was not reached.2 “These data are immature, but still are pretty impressive for the third-line setting and beyond,” Messersmith noted.

A majority of the treatment-emergent adverse effects (TEAEs) reported in this study were grade 1 or 2, many of them GI-related toxicities. The most common TEAEs included nausea, anemia, and decreased neutrophil count.

“These data are] not surprising given that you have an irinotecan-type of drug,” Messersmith said. “It shows that some of the payload is clearly getting into the circulation…. The idea is that there is a much higher amount of drug being delivered to the tumor site.”

Additionally, investigators observed 5 incidents of interstitial lung disease (ILD) during this study, 2 of which were grade 5. The median time to investigator-reported onset of these incidents was 80 days (range, 22-132), and all 5 patients were treated with corticosteroids. Two of the patients with ILD recovered and 1 did not recover and later died from disease progression. Two additional patient deaths were reported as a result of the TEAEs.

In the 2 patients with ILD, the onset of ILD ranged from 40 days to 126 days. Both received steroids as treatment, and death occurred 6 to 18 days after diagnosis. As a result, new protocol recommendations encourage monitoring for symptoms, and holding treatment of the ADC and...
starting steroids immediately if interstitial lung disease is suspected.

“[This agent showed] promising and durable activity. For a third-line response rate to be around 45% is pretty impressive,” Messersmith said. “[Also, we saw] a median PFS of around 7 months and we’re used to seeing a median PFS of less than 2 months in this population. This could be an option down the line as further data come out.”

Other HER2-targeted ADCs in development include A166, XMT-1522, MED1-4276, ARX788, RC48-ADC, BAT8001, and PF-06804103. “Nowadays, [these ADCs] are able to dial in the exact number of warheads per antibody, and as you do that, you seem to get a much better efficacy to toxicity ratio,” Messersmith said.

However, overexpression does not always equate to benefit with ADCs in GI cancers. For example, there have been many challenges with Trop2 targeting. Trop2 is a glycoprotein that was initially identified as a surface marker of trophoblast cells and has subsequently been found to be overexpressed in many solid tumors, including most GI cancers.°

Sacituzumab govitecan was examined in patients with GI cancers and only yielded 1 response; as such, the agent is not moving forward, Messersmith noted. Another agent, PF-06664178, also failed to elicit responses in this patient population. As such, further development of the agent for this purpose was stopped.

**RAS PATHWAY SIGNALING AND INHIBITION**

KRAS signaling can lead to multiple cellular-proliferation pathways, and this complexity and redundancy has made pathway targeting very complicated, according to Messersmith. As a result, many unsuccessful strategies have been reported over the past 15 years.°

“It is a very redundant and complex pathway to try to inhibit,” Messersmith explained. “There was this idea that maybe we could just inhibit downstream effector signals, such as a MEK inhibitor… but now we have more modern agents.”

One agent is adagrasib (MRTX849), a covalent inhibitor of KRAS G12C that irreversibly and selectively binds KRAS G12C in its inactive, GDP-bound state. The agent was optimized for desired properties of KRAS G12C inhibition, has high selectivity for the mutant KRAS G12C proteins vs wild-type KRAS, and has favorable pharmacokinetic properties. These include oral bioavailability, a long half-life, and extensive tissue distribution.°

Investigators examined adagrasib in patients with CRC as part of the phase 1 KRYS TAL-1 trial (NCT03785249). Data from the phase 1 portion of the research showed that adagrasib had clinical activity in patients with pretreated KRAS G12C-mutant CRC. For the trial, patients were treated with a standard-dose escalation, receiving up to 600 mg/kg of the agent twice daily.

The median follow-up for patients with CRC was 4.3 months. The confirmed ORR with adagrasib in patients with CRC was 17% (n = 18), and the disease control rate was 94%. The agent was fairly well tolerated; AEs included nausea, diarrhea and vomiting. These data, Messersmith noted, are still very early, but all patients enrolled to the study were still on treatment as of the August 2020 data cutoff.°

As a follow-up to this study, the phase 3 randomized, open-label KRYS TAL-10 trial (NCT04793958) will compare second-line adagrasib in combination with cetuximab (Erbitux) with chemotherapy in patients with metastatic KRAS G12C-mutant CRC. The primary outcome measures are PFS and OS and secondary outcome measures are safety, ORR per RECIST 1.1 criteria, DOR, and patient-reported outcomes. To be eligible for enrollment, patients must have metastatic CRC, confirmed KRAS G12C mutation, and have progressed on a first-line fluoropyrimidine-, oxaliplatin-, or irinotecan-based regimen.

**TKI AND IMMUNE CHECKPOINT INHIBITOR COMBINATIONS**

Combination regimens comprised of TKIs and immune checkpoint inhibitors have represented an interesting area of research in the GI cancer treatment paradigm, according to Messersmith. Initially, promising results were reported from a phase 1 trial (NCT01988896) examining the combination of atezolizumab (Tecentriq) and cobimetinib (Cotellic) in patients with solid tumors, including those with metastatic CRC.° However, data from the phase 3 COTEZO IMblaze370 trial (NCT02788279), which evaluated atezolizumab with or without cobimetinib vs regorafenib in patients with previously treated metastatic CRC, showed that the response rate achieved with the combination had dropped.°

Another trial, the phase 2 LEAP-005 (NCT03797326), examined the combination of lenvatinib (Lenvima) plus pembrolizumab (Keytruda) in 30 patients with previously treated advanced solid tumors. Primary end points for this study were ORR and safety. The GI cohorts in the trial included patients with third-line gastric cancer, third-line CRC, and second-line biliary tract cancer.°

Patients in the CRC cohort experienced an ORR of 21.9% (95% CI, 9.3%-40.0%) with the combination, whereas those in the gastric cancer cohort had an ORR of 9.7% (95% CI, 2.0%-25.8%). Patients in the biliary tract cancer cohort also had an ORR of 9.7% (95% CI, 2.0%-25.8%).

“I have seen these patients in the clinic, and we have had multiple... studies and investigator-initiated studies opened, and you definitely have patients who get these incredible responses,” Messersmith said. “Unfortunately, it is not the majority, so trying to figure out which of these patients is going to benefit [from this approach] is a key challenge.”

The median PFS was 2.5 months (range, 1.8-4.2) in the gastric cancer cohort, 2.3 months (range, 2.0-5.2) in the CRC cohort, and 6.1 months (range, 2.1-6.4) in the biliary tract cancer cohort. “Two-thirds of the [patients with third-line CRC] are progressing at the 3-month interval, but if you make it out to 3 or 4 months, your chance of making it out to 9 months is actually pretty good,” Messersmith noted.

One of the challenges in the field is determining how to preclinically evaluate novel combinations, but different models are under exploration, Messersmith concluded.

For a full list of references, see the article at bit.ly/3ZrR2OX.
Indication

VITRAKVI® (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

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

Important Safety Information

Neurotoxicity: Among the 176 patients who received VITRAKVI, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively. The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Please see additional Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information.
THE FIRST-IN-CLASS TRK® INHIBITOR FOR TRK FUSION CANCER ACROSS SOLID TUMORS

**Indication**
VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

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

**Important Safety Information (continued)**

**Neurotoxicity (continued):** Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dose when resumed.

**Hepatotoxicity:** Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Monitor liver tests, including AST and ALT, every 3 weeks from the final dose of VITRAKVI. The median time to onset of increased ALT was 2 months (range: 1 month to 2.6 years). The median time to onset of increased AST was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

**Embryo-Fetal Toxicity:** VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

**Most Common Adverse Reactions (≥20%):** The most common adverse reactions (≥20%) were: increased ALT (45%), increased AST (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%).

*TRK, tropomyosin receptor kinase.
*BIRC, blinded independent review committee; CR, complete response; DOR, duration of response; FDA, US Food and Drug Administration; IFS, infantile fibrosarcoma; NTRK, neurotrophic receptor tyrosine kinase; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
Select patients for treatment with VITRAKVI based on the presence of an NTRK gene fusion in tumor specimens. An FDA-approved test for NTRK gene fusion is not currently available.¹

**Study design:** 55 adult and pediatric patients with unresectable or metastatic solid tumors with an NTRK gene fusion were included for the pooled efficacy analysis across the multicenter, open-label, single-arm clinical studies: LOXO-TRK-14001, NAVIGATE, and SCOUT. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease.²

**Major efficacy outcome measures:** ORR and DOR, as determined by a BIRC according to RECIST version 1.1.²

**Important Safety Information (continued)**

**Drug Interactions:** Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John’s wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

**Lactation:** Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

Please see Brief Summary of full Prescribing Information on the following page.

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VITRAKVI® (larotrectinib) capsules, for oral use
VITRAKVI® (larotrectinib) oral solution
Initial U.S. Approval: 2018
BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:
• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,
• are metastatic or where surgical resection is likely to result in severe morbidity, and
• have no satisfactory alternative treatments or that have progressed following treatment.
This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Neurotoxicity
None.

4 CONTRAINDICATIONS
None.

5.2 Hepatotoxicity
Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients [see Adverse Reactions (6.1)]. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed [see Dosage and Administration (2.3)].

5.3 Embryo-Fetal Toxicity
Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, the doses observed in clinical trials. Pregnancy should be avoided during VITRAKVI treatment. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
• Neurotoxicity [see Warnings and Precautions (5.1)]
• Hepatotoxicity [see Warnings and Precautions (5.2)]

6.1 Clinical Trial 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.

Data in WARNINGS AND PRECAUTIONS and below reflect exposure to VITRAKVI in 176 patients, including 70 (40%) patients exposed for greater than 6 months and 35 (20%) patients exposed for greater than 1 year. VITRAKVI was studied in one adult dose-finding trial [LOXO-TRK-14001 (n = 70)], one pediatric dose-finding trial [SCOUT (n = 43)], and one single-arm trial [NAVIGATE (n = 63)]. All patients had an unresectable or metastatic solid tumor and no satisfactory alternative treatment options or disease progression following treatment.

Across the 176 patients, the median age was 51 years (range: 28 days to 82 years); 25% were 18 years or younger; 52% were male, and 72% were White, 11% were Hispanic/Latino, 8% were Black, and 3% were Asian. The most common solid tumors in order of decreasing frequency were soft tissue sarcoma (16%), salivary gland (11%), lung (10%), thyroid (9%), colon (8%), infantile fibrosarcoma (8%), primary central nervous system (CNS) (7%), or melanoma (5%). NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Most (70%) patients received VITRAKVI 100 mg orally twice daily and 56% of pediatric (18 years or younger) received VITRAKVI 100 mg/m² twice daily up to a maximum dose of 100 mg twice daily. The dose ranged from 30 mg daily to 200 mg twice daily in adults and 9.6 mg/m² daily to 12 mg/m² twice daily, daily in pediatrics [see Pediatric Use (8.4)].

The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, nausea, dizziness, vomiting, anemia, increased AST, cough, increased ALT, constipation, and diarrhea.

The most common serious adverse reactions (≥ 2%) were pyrexia, diarrhea, sepsis, abdominal pain, dehydration, cellulitis, and vomiting. Grade 3 or 4 adverse reactions occurred in 51% of patients; adverse reactions leading to dose interruption or reduction occurred in 37% of patients and 13% permanently discontinued VITRAKVI for adverse reactions.

The most common adverse reactions (1-2%) each that resulted in discontinuation were VITRAKVI were brain edema, intestinal perforation, pericardial effusion, pleural effusion, small intestinal obstruction, dehydration, fatigue, increased ALT, increased AST, enterocutaneous fistula, increased amylase, increased lactate, muscular weakness, abdominal pain, asthenia, decreased appetite, dyspnea, hyponatremia, jaundice, syncope, vomiting, acute myeloid leukemia, and nausea.

The most common adverse reactions (≥ 3%) resulting in dose modification (interruption or reduction) were increased ALT (8%), increased AST (6%), and dizziness (3%). Most (82%) adverse reactions leading to dose modification occurred during the first three months of exposure.

Adverse reactions of VITRAKVI occurring in ≥ 10% of patients and laboratory abnormalities worsening from baseline in ≥ 5% of patients are summarized in Table 2 and Table 3, respectively.

Table 2 Adverse Reactions Occurring in ≥ 10% of Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades*</th>
<th>Grade 3-4**</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>0</td>
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<tr>
<td>Dyspnea</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>15</td>
<td>4</td>
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<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>1</td>
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<tr>
<td>Myalgia</td>
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<td>1</td>
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<tr>
<td>Muscular weakness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

* Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 170 to 174 patients.
** One Grade 4 adverse reaction of pyrexia.

Table 3 Laboratory Abnormalities Occurring in ≥ 5% of Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades**</th>
<th>Grade 3-4**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Hypophysalmmaturity</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>10</td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 170 to 174 patients.

* NCI-CTCAE v 4.03.
The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in clinical studies section. The safety of VITRAKVI was evaluated in 44 pediatric patients who received VITRAKVI. Of these 44 patients, 27% were 1 month to <2 years (n = 12), 43% were 2 years to <12 years (n = 19), and 30% were 12 years to <18 years (n = 13). 42% had metastatic disease and 57% had locally advanced disease; and 91% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common concomitant medications were infraorbital sinusoma (25%), soft tissue sarcoma (25%), primary CNS tumors (20%), and thyroid cancer (9%). The median duration of exposure was 5.4 months (range: 9 days to 1.9 years).

Due to the small number of pediatric and adult patients, the single-arm design of clinical studies of VITRAKVI, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to VITRAKVI are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients compared to adult patients were increased weight (11% vs. 2%) and neutropenia (20% vs. 2%). One of the 44 pediatric patients discontinued VITRAKVI due to an adverse reaction (Grade 3 increased ALT).

Larotrectinib was administered in a juvenile toxicity study in rats at twice daily doses of 0.2, 2 and 7.5 mg/kg from postnatal day (PND) 7 to 27 and at twice daily doses of 0.6, 6 and 22.5 mg/kg between PND 28 and 70. The dosing period was equivalent to human pediatric populations from newborn to adulthood. The doses of 2/6 mg/kg twice daily (approximately 0.7 times the human exposure [AUC] at the clinical dose of 100 mg twice daily) and 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily) resulted in mortality between PND 9 to 99; a definitive cause of death was not identified in the majority of cases. The main findings were transient central nervous system-related signs including somnolence, tremor, ataxia, and circling in both sexes. An increase in the number of errors in a maze swim test occurred in females at exposures of approximately 4 times the human exposure (AUC) at the clinical dose of 100 mg twice daily. Decreased growth and delays in sexual development occurred in the mid- and high-dose groups of the males. Mating was normal in treated animals, but a reduction in pregnancy rate occurred at the high dose of 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily).

7.2 Effects of VITRAKVI on Other Drugs
Sensitive CYP3A4 Substrates
Co-administration of VITRAKVI with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with sensitive CYP3A4 substrates. If co-administration of these sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryofetal harm when administered to a pregnant woman. There are no available data on VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats during the period of organogenesis resulted in malformations at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily [see Data]. Advise pregnant women of the potential risk to a fetus.

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

Data

Human Data
Published reports of individuals with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryo-fetal toxic effects. The pharmacokinetics of VITRAKVI in the pediatric population were similar to those seen in adults [see Clinical Pharmacology (12.3)].

Juvenile Animal Toxicity Data
Larotrectinib was administered in a juvenile toxicity study in rats at twice daily doses of 0.2, 2 and 7.5 mg/kg from postnatal day (PND) 7 to 27 and at twice daily doses of 0.6, 6 and 22.5 mg/kg between PND 28 and 70. The dosing period was equivalent to human pediatric populations from newborn to adulthood. The doses of 2/6 mg/kg twice daily (approximately 0.7 times the human exposure [AUC] at the clinical dose of 100 mg twice daily) and 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily) resulted in mortality between PND 9 to 99; a definitive cause of death was not identified in the majority of cases. The main findings were transient central nervous system-related signs including somnolence, tremor, ataxia, and circling in both sexes. An increase in the number of errors in a maze swim test occurred in females at exposures of approximately 4 times the human exposure (AUC) at the clinical dose of 100 mg twice daily. Decreased growth and delays in sexual development occurred in the mid- and high-dose groups of the males. Mating was normal in treated animals, but a reduction in pregnancy rate occurred at the high-dose of 7.5/22.5 mg/kg twice daily (approximately 4 times the human exposure at the clinical dose of 100 mg twice daily).

8.2 Lactation

Risk Summary
There are no data on the presence of larotrectinib or its metabolites in human milk and no data on its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with larotrectinib and for 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating VITRAKVI [see Use in Specific Populations (8.1)].

Contraception
VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Females
Advise female patients of reproductive potential to use effective contraception during treatment with VITRAKVI and for at least 1 week after the final dose.

Males
Advise males with female partners of reproductive potential to use effective contraception during treatment with VITRAKVI and for 1 week after the final dose.

Infertility
Females
Based on histopathological findings in the reproductive tracts of female rats in a 1-month repeated-dose study, VITRAKVI may reduce fertility [see Nonclinical Toxicology (13.1)].

Males
Based on histopathological findings in the reproductive tracts of male rats in a 1-month repeated-dose study, VITRAKVI may reduce fertility [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in adult or pediatric patients 28 days and older [see Adverse Reactions (6.1), Clinical Studies (14)].

The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was evaluated in 44 pediatric patients who received VITRAKVI. Of these 44 patients, 27% were 1 month to <2 years (n = 12), 43% were 2 years to <12 years (n = 19), and 30% were 12 years to <18 years (n = 13). 42% had metastatic disease and 57% had locally advanced disease; and 91% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common concomitant medications were infantile fibrosarcoma (25%), soft tissue sarcoma (25%), primary CNS tumors (20%), and thyroid cancer (9%). The median duration of exposure was 5.4 months (range: 9 days to 1.9 years).

Due to the small number of pediatric and adult patients, the single-arm design of clinical studies of VITRAKVI, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to VITRAKVI are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients compared to adult patients were increased weight (11% vs. 2%) and neutropenia (20% vs. 2%). One of the 44 pediatric patients discontinued VITRAKVI due to an adverse reaction (Grade 3 increased ALT).

7 DRUG INTERACTIONS
7.1 Effects of Other Drugs on VITRAKVI

Strong CYP3A4 Inhibitors
Co-administration of VITRAKVI with a strong CYP3A4 inhibitor may increase larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If co-administration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

Strong CYP3A4 Inducers
Co-administration of VITRAKVI with a strong CYP3A4 inducer may decrease larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inducers, including St. John’s wort. If co-administration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.5)].
ctDNA Analysis Has the Potential to Revolutionize Care in CRC and Beyond

by HAYLEY VIRGIL

INVESTIGATORS ARE LOOKING AT circulating tumor DNA (ctDNA) as a means of transforming care in colorectal cancer (CRC) and other tumor types. Persistent ctDNA positivity following surgery is one of the strongest poor prognostic factors available, according to Axel Grothey, MD. The marker also possesses positive predictive value for disease recurrence.

“ctDNA is going to change the way we monitor and treat patients,” said Grothey, a medical oncologist and director of Gastrointestinal Cancer Research at West Cancer Center & Research Institute, during a presentation at the 6th Annual School of Gastrointestinal Oncology*. “ctDNA is not perfect, but it lowers the threshold of where we can detect tumor burden in a patient better than with imaging scans; this is an important point, because we see limitations in tumor detection by imaging. This will change how we approach treatment decisions for patients with cancer, not just in the treatment of established cancer by monitoring minimal residual disease [MRD], but also in diagnosis and population screening.”

EXAMINING ctDNA AS A MARKER FOR MRD
Two types of tests can be used to assess ctDNA as a marker for MRD: tumor-agnostic and tumor-informed assays. Tumor-agnostic approaches use a next-generation sequencing (NGS) or a polymerase chain reaction (PCR) panel or methylation markers to identify common mutations in patients with CRC. Although these approaches may be easier to use logistically, they can have a lower sensitivity. Tumor-informed approaches, on the other hand, can detect mutations in the primary tumor via NGS or PCR; this can be done with tests such as the Signatera Blood Test. These tend to present more logistical complications, but they have a high sensitivity and specificity, according to Grothey.

He highlighted a study in which investigators used a tumor-informed assay to examine whether the detection of MRD correlated with disease stage.2 Patients with stage II, T3N0 CRC (n = 53) had a postsurgery MRD rate of 5.6% compared with 28.6% in patients with stage II, T4N0 disease (n = 14). Moreover, patients with stage III, low-risk T1-3N1 CRC (n = 32) had a postsurgery MRD rate of 9.3% vs 39.4% in patients with stage III, high-risk T4, N1-2, T any; N2 disease following surgery (n = 38).

“This is important because we know it has consequences,” Grothey said. “The presence of ctDNA after surgery is associated with an almost guaranteed recurrence.”

In another study, investigators performed a ctDNA analysis to detect MRD and predict recurrence in patients with stage II colon cancer. Data indicated that among patients who did not receive treatment with adjuvant chemotherapy, those who were ctDNA negative following surgical resection (n = 164) had a 3-year recurrence-free survival (RFS) rate of 90%.3 All patients who tested positive for ctDNA following surgery (n = 14) experienced disease recurrence within 3 years (HR, 18; 95% CI, 7.9-40; P < .001). “This hazard ratio was highly statistically significant,” noted Grothey.

Moreover, among patients who were clinically low risk, defined as mismatch repair proficient (pMMR) or deficient (dMMR) with no prognostic features, those who tested negative for postoperative ctDNA (n = 122) had a higher RFS than those who tested positive for ctDNA (n = 7; HR, 28; 95% CI, 8.3-93; P < .001). Similarly, among patients who were clinically high risk, defined as pMMR with at least 1 poor prognostic feature, those who were ctDNA negative also had a higher RFS compared with those who were ctDNA positive (HR, 7.5; 95% CI, 2.6-22; P < .001).

“Even if you adjust for high-risk and low-risk factors, you can still see that the presence of ctDNA is highly predictive of what’s going to happen with a patient,” Grothey explained. “It’s clearly a very strong prognostic marker.”

When considering ctDNA and 3-year recurrence prediction, there is a 100% positive predictive value with the test, Grothey noted. Of the 8% of patients who were ctDNA positive, all had disease recurrence within 3 years. On the other hand, the negative predictive value is also strong at 91%.

“There is hardly a test in medicine where you have such strong negative and positive predictive values as with using ctDNA,” Grothey said. “We’ve seen the same biologic principle in breast cancer, melanoma, lung cancer, bladder cancer, and so on. We are generating a lot of data in many malignancies…. One of the critical issues—and this is a very important point—is, does it mean anything and can we reverse the poor prognosis?”

cDNA AND ADJUVANT THERAPY IN LATER-STAGE CRC
One study examined the predictive value of ctDNA with regard to outcomes in 96 patients with stage III colon cancer who had received adjuvant treatment.4 Similar to patients with earlier-stage disease, those who were negative for postoperative ctDNA had a higher RFS vs those who were ctDNA positive (HR, 3.8; 95% CI, 2.4-21.0; P <.001).

“Patients with [negative] postoperative ctDNA, of course, do better than [those with] positive ctDNA,” Grothey explained. “These are only 96 patients, 20 [of whom] were positive. It’s not a strong database; [these are] not prospective, randomized, or retrospective data…. Positive ctDNA was not 100% predictive of tumor recurrence within the first 2 to 3 years…. It means we can salvage some patients; we do not always see tumor recurrence in the context of adjuvant therapy.”
Patients who tested negative for ctDNA following treatment with chemotherapy similarly had better outcomes vs ctDNA-positive patients (HR, 6.8; 95% CI, 11.0-157.0; P < .001).

“The predictive value of ctDNA becomes ever stronger when you look at patients after chemotherapy. If patients stayed positive with ctDNA, they have a poorer prognosis than patients who are negative,” Grothey said. “The conversion rate of patients who transition from being ctDNA positive to negative have better outcomes than if they stayed positive over time [HR, 3.7; 95% CI, 1.1-17.0; P = .04].”

Additionally, patients who went from being ctDNA negative to positive experienced poorer outcomes (HR, 6.5; 95% CI, 7.2-642.0; P < .001). “As such, there is a treatment effect on ctDNA with consequence,” Grothey noted.

In a more recent analysis presented during the 2021 Gastrointestinal Cancers Symposium, investigators attempted to classify patients with CRC as being at a higher or lower risk of recurrence based on the presence of MRD. They also set out to assess the risk of relapse following treatment in patients who were ctDNA positive and determine the lead time of ctDNA detection vs computerized tomography (CT) recurrence. Tumor tissue samples were collected after surgery, and patients were followed for 3 years. Subsequently, the investigators collected plasma samples every 3 months, and performed DNA exome sequencing and ctDNA assays on both tumor tissue and plasma samples. Patients received CT scans at 12 months and 36 months.

In total, investigators analyzed 260 patients, 165 of whom had received adjuvant treatment, at a median follow-up of 29.9 months in nonrelapsed patients (n = 212). Patients had stage I (n = 4), II (n = 90), or III (n = 166) disease.

Results indicated that patients who were ctDNA negative had a higher RFS than those who were ctDNA positive (HR, 11; 95% CI, 5.9-21; P < .0001). Eighty-seven percent of patients who were negative for ctDNA did not experience relapse compared with 20% of those who were ctDNA positive.

After adjuvant chemotherapy, patients who were ctDNA negative had a higher RFS; 87.5% did not relapse compared with 16.7% of those who were ctDNA positive (HR, 12; 95% CI, 4.9-27; P < .0001). Longitudinal monitoring yielded similar results, with 96.6% of patients who were ctDNA negative not experiencing relapse vs 10.7% of those who were ctDNA positive (HR, 51; 95% CI, 20-125; P < .001).

**ADDRESSING QUESTIONS ABOUT ctDNA AND ADJUVANT THERAPY**

According to Grothey, several questions regarding ctDNA and adjuvant therapy still need to be answered (FIGURE). Clinical trials seeking to address these unmet clinical queries are ongoing. Grothey elaborated on 1 particular concept regarding ctDNA-based adjuvant therapy.

“[What do you do with] a patient who has already had surgery, radiation therapy, or adjuvant chemotherapy and how do you utilize ctDNA?” he asked. “You could use the test as a screening tool, and randomize patients to have a test or not have a test, to then treat those patients who are ctDNA positive with an intensification of treatment, whether it’s chemotherapy or targeted agents.”

However, in some cases, such as in patients with low-risk stage II cancers, adjuvant treatment may not be administered, according to Grothey. Here, patients could be randomized to have a test or not. Then, investigators could then use ctDNA positivity to determine if a patient should receive adjuvant treatments such as 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and capcitabine and oxaliplatin (CAPOX).

For example, in the ongoing phase 2/3 COBRA trial (NCT04068103), patients with resected microsatellite stable (MSS), stage II colon cancer (n = 1408) will be randomized to either be tested for ctDNA to determine whether adjuvant chemotherapy is needed or undergo standard-of-care observation. Patients who test positive will receive adjuvant FOLFOX and those who are ctDNA negative will be placed under observation.

“This is a test that will tell us prospectively whether patients will benefit from ctDNA-based adjuvant treatment in the MRD setting,” Grothey said.

For patients with stage III CRC, adjuvant therapy is typically used, according to Grothey. In this case, there may be opportunities to escalate standard treatments in those who are ctDNA positive and opportunities to de-escalate such treatments in those who are ctDNA negative. To this end, various concepts are under consideration.

“We actually have just recently approved the ctDNA-informed study CIRCULATE-US or NRG-GI 008, a collaboration between NRG Oncology and SWOG. It will address these different components in stage III colon cancer,” Grothey said.

In the study, patients with T1-3, N1 stage III colon adenocarcinoma will be stratified based on their ctDNA status. Patients who are ctDNA negative will be randomized to a CAPOX or FOLFOX regimen per investigator decision or to serial monitoring of ctDNA over the course of 2 years to determine whether they remain negative. If patients become ctDNA positive, they will go on to receive a FOLFOX or CAPOX regimen or treatment with folinic acid, 5-FU, oxaliplatin, and irinotecan for 6 months in the adjuvant setting.

“That’s not a large study, but it really tries to establish the proof of principle...
using ctDNA as a decision marker for when and how to treat patients. I’m really excited about the de-escalation [portion of the research],” Grothey said. “There’s the idea of eventually correlating this with disease-free survival because that is currently the primary end point of adjuvant studies.”

A similar concept is under investigation in the Australian phase 2/3 DYNAMIC-III study (ACTRN12617001566325).10 Patients with stage III disease who have undergone surgery will be randomized based on clinical risk factors to receive either standard of care (n = 500), which will be clinician’s choice of no chemotherapy; 6 months of 5-FU and capecitabine, or 3 to 6 months of FOLFOX or CAPOX; or a ctDNA-informed approach (n = 500).

“For [patients who are] ctDNA negative, you de-escalate. For instance, you can go from just using fluoropyrimidine to no treatment or a shorter treatment, you go from FOLFOX to just 5-FU or capecitabine, and you go from 6 months to 3 months of deescalation in intensity or duration,” Grothey explained. “You can also escalate in the ctDNA-positive group, where you go from no chemotherapy planned to just fluoropyrimidine. You go just 1 step up, which I believe to be a brilliant design. I hope they have enough power in these 1000 patients to really answer these questions that are being asked.”

Additionally, in the phase 3 Stand Up To Cancer ACT3 study (NCT03803553), 11 patients with stage III colon cancer are being tested for ctDNA following adjuvant therapy. Investigators will stratify them based on whether they are ctDNA positive or negative. Patients will be screened for microsatellite instability (MSI), MSS, and BRAF mutations and appropriately treated based on those results. Those who do not have actionable mutations will receive 5-FU, leucovorin, and irinotecan, whereas those whose tumors are BRAF mutated will receive encorafenib (Braftovi), binimetinib (Mektovi), and cetuximab (Erbitux). Patients who are MSI-high will receive nivolumab (Opdivo).

“This is a trial that will try to move immunotherapy and targeted therapy to a select patient population that is ctDNA positive and has actionable tumors,” Grothey noted.

PUTTING EVERYTHING INTO PERSPECTIVE
“We know that the consistent presence of ctDNA after surgery is the strongest poor prognostic factor that we have; this is more important than T stage or N stage. We also know that when you use adjuvant therapy, you decrease the likelihood of cancer recurrence in the ctDNA-positive [population]. It’s not a point of no return,” Grothey concluded. “ctDNA positivity is actionable at this time. Some patients [who] have a positive test [can] turn negative and stay negative. The easiest situation that we can potentially act on right now is a situation where you do not recommend adjuvant therapy based on conventional risk factors, but if ctDNA is present, it could lead to the use of adjuvant therapy.”

Racial Disparities Persist in GI Cancers and Beyond
“Racial disparities in health care are well documented and [extend] back to the start of this country,” explained Noel, an associate professor of medicine at Georgetown Lombardi Comprehensive Cancer Center and codirector of the clinical research management office at Georgetown University Medical Center in Washington, DC. Study findings have shown that racial and ethnic minorities receive a lower quality of health care even when income and access are taken into consideration. Screening rates for cancer are lower in minority patients and death rates due to disease are disproportionately high, Noel added.

Between 2010 and 2016, the 5-year relative survival rate for White patients across cancer types was 68%, compared with 62% for Black patients. Overall cancer incidence rates for Black men were the highest reported at 540 per 100,000 population, compared with 501.2 per 100,000 for White men. Further, the mortality rates for all cancer sites combined were 186.4 per 100,000 for Black patients vs 162.9 per 100,000 for White patients.
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Long-Term Neoadjuvant Study Tests Nivolumab in ER+/HER2- Breast Cancer

by DENISE MYSHKO

INVESTIGATORS ARE EVALUATING THE addition of nivolumab (Opdivo) to standard neoadjuvant therapy in patients with high-risk, estrogen-receptor (ER)-positive/HER2-negative breast cancer to determine whether the PD-1 immune checkpoint inhibitor can improve recurrence rates. CheckMate 7FL (NCT04109066) is a large, long-term phase 3 trial comparing the efficacy of chemotherapy with either nivolumab or placebo in treatment-naive patients, followed by surgery and adjuvant therapy.1,2

The combination of PD-1 inhibition and chemotherapy has demonstrated promising response rates and antitumor activity across breast cancer subtypes in early clinical findings, investigators said. The biology of ER-positive, HER2-negative disease also suggests that the combination strategy may mitigate tumor inflammation and, therefore, resistance to endocrine therapy. 1,2

“What we’ve learned from checkpoint blockade is that the earlier on you apply these strategies in the course of disease, the more likely they are to be effective,” Heather L. McArthur, MD, MPH, a leading investigator in the study, said in an interview with OncologyLive®. “Given the success that we’ve seen in triple-negative disease, with a signal that we are actually improving cure rates with these types of strategies, makes me very excited about this approach.”

Findings from the I-SPY 2 trial (NCT01042379) showed that adding a checkpoint inhibitor to neoadjuvant chemotherapy prior to surgery could improve pathologic complete response (pCR) rates, said McArthur, medical director of breast oncology at Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center in Los Angeles, California. The I-SPY trials are designed to rapidly screen promising experimental treatments and identify those most effective in specific patient subgroups based on biomarker signatures.

“Historically, it has been very difficult to improve pCR for ER-positive disease. Many of us were very excited to see the I-SPY 2 data and to see that magnitude of impact on estimated pCR because that was really unprecedented. This generated a lot of enthusiasm for these large phase 3 studies,” McArthur said.

An interim analysis of I-SPY 2 results released in February 2020 found that estimated pCR rates had more than doubled for patients who received pembrolizumab (Keytruda), a PD-1 inhibitor, plus chemotherapy (n = 69) vs standard neoadjuvant chemotherapy (n = 181).

The pCR rates were 44% for patients who were HER2 negative, 30% for those with hormone receptor–positive/HER2-negative disease, and 60% for those with triple-negative breast cancer (TNBC) compared with 17%, 13%, and 22%, respectively, with standard chemotherapy.3

FIGURE. CheckMate 7FL Study Design: Nivolumab in Neoadjuvant Breast Cancer Treatment1,2

Eligibility criteria
- Newly diagnosed confirmed high-risk* ER-positive, HER2-negative breast cancer
- Tumor grade 3 or grade 2 with ER expression 1% to 10%
- ECOG PS 0 to 1
- ECOG PS 0 to 1
- Tissue available for biomarker assessments

Randomization (1:1)

Stratification factors
- PD-L1 expression on tumor-infiltrating immune cells (< 1% or ≥ 1%)
- Tumor grade (2 or 3)
- Axillary nodal status (+ or -)
- AC (Q3W or Q2W)

Neoadjuvant phase
- Paclitaxel cycles 1 to 4 (1 cycle = 3 weeks) followed by AC cycles 1 to 4 (1 cycle = 2 or 3 weeks)**
- Paclitaxel 80 mg/m² QW
- Paclitaxel 360 mg Q3W
- Nivolumab 240 mg Q2W + AC Q2W**
- Nivolumab 360 mg Q3W + AC Q3W**
- Investigator’s choice ET

Adjuvant phase
- AC cycles 1 to 4
- Placebo cycles 1 to 4
- Paclitaxel cycles 1 to 4
- Nivolumab cycles 1 to 4
- Placebo cycles 1 to 4
- Nivolumab cycles 1 to 4
- Placebo cycles 1 to 4
- Nivolumab cycles 1 to 4
- Investigator’s choice ET

Surgery

Safety
- • 30 days
- • 100 days
- • 10 years
- Long-term follow-up
- • Up to 10 years

AC, anthracycline plus cyclophosphamide; ECOG, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

*High-risk disease is defined as either grade 3 (poorly differentiated disease) with ER expression ≥ 1% or grade 2 (moderately differentiated) disease with low ER expression 1% to 10%.

**Dosing frequency per investigator.

*Anthracycline choice of doxorubicin 60 mg/m² or epirubicin 90 mg/m²

*Cyclophosphamide 600 mg/m²

*ET agents include tamoxifen, anastrozole, letrozole, and exemestane at approved/indicated doses. ET may continue for up to 10 years.
Moreover, I-SPY 2 investigators said achieving a pCR appeared predictive of long-term benefit. Patients who reached pCR following pembrolizumab plus chemotherapy had a 93% event-free survival (EFS) rate at 3 years with 2.8 years’ median follow-up.

There was a 99% predictive probability that pembrolizumab plus neoadjuvant chemotherapy resulted in significantly better outcomes than chemotherapy alone in a phase 3 randomized clinical trial in patients with HER2-negative breast cancer.

Investigators anticipate that nivolumab would perform similarly to pembrolizumab in this patient population, according to McArthur. “They seem to be comparable in other disease types such as metastatic melanoma, for example. There is no reason to suggest that there would be any significant meaningful differences between the strategies.”

McArthur said clinical experience with nivolumab in breast cancer is limited, but that findings from at least one study suggest the agent can be effectively combined with chemotherapy. In the phase 2 TONIC trial (NCT02499367), nivolumab with or without various induction therapies including chemotherapy demonstrated objective response rates (ORR) ranging from 17% to 35%, depending upon the cohort, in patients with metastatic TNBC.4

Ultimately, McArthur said, her hope for patients with breast cancer is “that with rational biologic strategies, we will actually be able to minimize the amount of cytotoxic therapy that we ultimately need to administer to achieve cure. The majority of the toxicity with these regimens comes from the chemotherapy backbone.”

CHECKMATE 7FL STUDY DETAILS

In CheckMate 7FL, investigators are seeking to recruit 1200 patients at 225 sites in 25 countries. To be eligible, patients must have a new diagnosis of high-risk HER2-negative breast cancer, defined as either grade 3 (poorly differentiated) with ER expression of 1% or greater or grade 2 (moderately differentiated) with low ER expression of 1% to 10%. Participants must have confirmed locally invasive breast ductal carcinoma characterized as either T1c-T2 (tumor size, ≥ 2 cm), clinical node (cN) stage 1 to cN2, or T3-T4, cN0-cN2 (FIGURE).1,2

The trial is open to patients regardless of PD-L1 expression status but findings will be stratified based on the biomarker (< 1% or ≥ 1%). “As a community, we are very interested in identifying markers that predict a response and for toxicity,” McArthur said. “PD-L1 has been the most helpful biomarker so far in triple-negative disease. This is not required for enrollment in the study, but it is a stratification factor and will be interrogated retrospectively in relationship to clinical responses.”

Patients will also be stratified by axillary nodal status (positive or negative), tumor grade (2 or 3), and anthracycline plus cyclophosphamide schedule (every 3 weeks or every 2 weeks).

The primary end points are pCR, defined as no invasive residual disease in breast and lymph nodes (ypT0/is, ypN0), and EFS, defined as the time from randomization to disease progression.

Secondary end points include overall survival, disease-free survival, distant metastasis-free survival, overall response rate, safety and tolerability, and quality of life and physical functioning.

CheckMate 7FL is a long-term study with an estimated completion date of June 20, 2032. “A phase 3 study with a coprimary end point of EFS typically has to be on the longer side,” McArthur noted. “More follow-up is needed because, with ER-positive disease, recurrences can happen late, which is different from triple-negative disease where recurrences typically occur within 2 to 3 years.”

In the neoadjuvant phase of the study, patients will receive 8 cycles of treatment, consisting of 4 cycles with nivolumab 360 mg or placebo every 3 weeks plus weekly paclitaxel at 80 mg/m², then 4 cycles of nivolumab at either 360 mg every 3 weeks or 240 mg every 2 weeks plus anthracycline and cyclophosphamide.

After surgery, patients will receive up to 7 cycles (every 4 weeks) of adjuvant treatment with nivolumab 480 mg or placebo in combination with investigator’s choice of endocrine therapy, including tamoxifen, anastrozole, letrozole, or exemestane at approved doses.

ANOTHER NOVEL COMBINATION

Investigators are also studying nivolumab in the neoadjuvant setting in combination with palbociclib (Ibrance), a CDK4/6 inhibitor, and ER-targeted therapy in postmenopausal women and men with ER-positive/HER2-negative primary breast cancer in the phase 2 CheckMate 7A8 study (NCT04075604).

Patients will receive nivolumab plus palbociclib and anastrozole during a safety run-in phase and will then be randomized to 1 of 3 treatment groups. Arms A and B will test the 3-drug combination on 2 different schedules and arm C will evaluate palbociclib plus anastrozole.3

Investigators are seeking to recruit 136 patients at 66 worldwide trial sites. Patients will be stratified by PD-L1 expression, node status, and tumor size. Following treatment, all patients will undergo surgery and safety follow-up.

Primary end points are number of patients with occurrence of dose-limiting toxicity in the safety run-in phase and the residual cancer burden rate at time of surgery in the randomized phase. Secondary end points include safety and tolerability, pCR rate, ORR, and breast-conserving surgery rate.

For a full list of references, see the article at OncLive.com.
Clinical Perspectives | UROTHELIAL CANCER

Novel Targeted and Immunotherapeutic Agents Reshape Metastatic Urothelial Cancer Landscape

by HAYLEY VIRGIL

TREATMENT OPTIONS FOR PATIENTS with metastatic urothelial cancer (mUC) have rapidly expanded, as FDA approvals of immunotherapeutics push the boundaries of a once-stagnant treatment landscape. Combination regimens and the addition of targeted approaches, including the pan-FGFR tyrosine kinase inhibitor erdafitinib (Balversa), further demonstrate progress in areas that have been tough to crack, according to Daniel P. Petrylak, MD, who presented an overview of the field during New York GU™: 14th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies.

Although predictive biomarkers remain an unmet clinical need in the treatment of patients with mUC, studies evaluating the combination of checkpoint inhibition with targeted therapies, as well as results from basket trials including patients with mUC may help investigators overcome these hurdles. Patients have continued to benefit from maintenance therapies utilizing immune checkpoint inhibitors (ICIs); however, recent reviews of confirmatory data have led to restricted labels and more critical FDA oversight.

FGFR: A PROMISING TARGET

“FGFR3 expression is detected in 10% to 20% of patients,” said Petrylak, a professor of medicine and urology, director of the Genitourinary Translational Working Group, and codirector of the Signal Transduction Program at Yale University’s Smilow Cancer Center in New Haven, Connecticut. “The drug that goes along with that expression is erdafitinib.”

The FDA granted accelerated approval to erdafitinib in April 2019 for the treatment of adult patients with locally advanced UC or mUC with an FGFR3 or FGFR2 alteration who have progressed on platinum-containing chemotherapy. The approval was based on the results of the phase 2 BLC2001 study (NCT02365597), which examined the agent in patients with mUC or surgically unresectable, locally advanced UC.

Patients who received erdafitinib achieved an overall response rate (ORR) of 40.4% (n = 40; 95% CI, 30.7%-50.1%), a median time to response of 1.4 months, and a median duration of response (DOR) of 5.6 months (95% CI, 4.2-7.2). Additionally, patients achieved a median progression-free survival (PFS) of 5.5 months (95% CI, 4.2-6.0), as well as a median overall survival (OS) of 13.8 months (95% CI, 9.8-not estimable [NE]). At a follow-up of 11 months, 21.2% of patients continued to receive treatment with erdafitinib.

ICIs MAY REQUIRE A CLOSER LOOK

Approved ICIs—including pembrolizumab (Keytruda; approved in May 2017), nivolumab (Opdivo; approved in February 2017), and, most recently, avelumab (Bavencio)—have all made headway as treatment options for patients with mUC. Although these options remain on the market, the FDA has restricted the use of both pembrolizumab and atezolizumab (Tecentriq) after follow-up data failed to support initial findings.

In July 2018, the FDA issued an alert notifying the urology community that patients who had PD-L1-low disease as specified by the threshold of the trials had decreased survival compared with patients who had received chemotherapy. As a result of this alert, the phase 3 KEYNOTE-361 trial (NCT02853305), examining the use of pembrolizumab with or without platinum-based chemotherapy, and the phase 3 IMvigor130 trial (NCT02807636), which looked at atezolizumab (Tecentriq) with or without platinum-based chemotherapy in patients with untreated, locally advanced UC or mUC, stopped enrolling patients with PD-L1-low disease in the monotherapy arms. The FDA updated the prescribing information for both drugs to require use of an FDA-approved test for selection of patients being treated in the first-line setting who are cisplatin ineligible.

Other accelerated approvals are following a similar pattern in mUC. Two indications—one for each atezolizumab and pembrolizumab, respectively—were reviewed as part of a 3-day public hearing by the FDA’s Oncologic Drugs Advisory Committee in April (TABLE).

Prior to the hearings developers of atezolizumab and durvalumab (Imfinzi) voluntarily withdrew indications based on confirmatory trial results that did not demonstrate significant improvements in OS in patients with mUC. Roche voluntarily withdrew the indication for atezolizumab in patients with prior platinum-treated mUC following the release of results of the phase 3 IMvigor211 trial (NCT02302807).

Similarly, AstraZeneca, the developer of the ICI durvalumab, voluntarily withdrew the FDA indication for the agent’s use in previously treated patients with locally advanced UC or mUC. This decision followed the release of results of the confirmatory trial DANUBE (NCT02516241), which failed to meet both primary end points.

MAINTENANCE IMMUNOTHERAPY FOR PD-L1-POSITIVE PATIENTS

Despite the turnover in accelerated approvals, avelumab has carved out a role as a maintenance therapy for patients based on results of the phase 3 JAVELIN Bladder 100 trial (NCT02603432). Investigators enrolled patients with unresectable, locally advanced UC or mUC who had achieved a complete response (CR), partial response (PR), or stable disease after 4 to 6 cycles of first-line cisplatin plus gemcitabine or carboplatin plus gemcitabine. Patients were randomized to receive either avelumab plus best supportive care (BSC) or BSC alone. Notably,
55% of patients in the overall population and 47% of patients who were PD-L1 positive had visceral metastases at baseline across all arms of the study.

In the overall patient population, patients in the avelumab arm achieved a median OS of 21.4 months (95% CI, 18.9-26.1) compared with 14.3 months in the BSC arm (95% CI, 12.9-17.9; HR, 0.69; 95% CI, 0.56-0.86; \( P < .001 \)). In the PD-L1-positive patient population, the avelumab arm’s median OS was NE (95% CI, 20.3-NE) vs 17.1 months (95% CI, 13.5-23.7) in the BSC arm.

According to the study authors, an OS benefit was observed across all subgroups included in the study. Additionally, the regimen helped to improve median PFS in the avelumab arm (3.7 months; 95% CI, 3.5-5.5) vs the BSC arm (2.0 months; 95% CI, 1.9-2.7; HR, 0.62; 95% CI, 0.52-0.75; \( P < .001 \)).

However, investigators noted that avelumab yielded a low ORR in both the overall population (9.7%; 95% CI, 6.8%-13.1%) and the PD-L1-positive population (13.8%; 95% CI, 9.2%-19.5%).

**ADCs MAKE THEIR MARK**

Petrylak discussed 2 antibody-drug conjugates (ADCs)—enfortumab vedotin-ejfv (Padcev) and sacituzumab govitecan-hziy (Trodelvy)—that have been associated with promising efficacy data. “Enfortumab vedotin in phase 2 and 3 studies, and sacituzumab govitecan, in phase 2 studies, have promising activity in patients who have progressed on 2 or more prior lines of therapy,” Petrylak said. “Enfortumab vedotin has accelerated approval and we hope that the FDA will grant a full approval this year.”

Enfortumab vedotin was granted an accelerated approval by the FDA in December 2019 for patients with advanced UC or mUC based on the results of the phase 2 EV-201 trial (NCT032193333).\(^{11,12} \) Patients who received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy experienced an ORR of 44% (95% CI, 35.1%-53.2%), including a CR rate of 12% and a PR rate of 32%.

According to the authors of the study, similar responses were observed across all patient subgroups, including those with liver metastases and those who had not experienced a response to prior PD-1 and PD-L1 therapies. Notably, patients who had received prior ICIs had a confirmed CR rate of 3.4%, a confirmed PR rate of 37%, and an ORR of 40.4% (95% CI, 30.2%-51.4%). Patients also achieved a disease control rate of 74% (95% CI, 63.8%-82.9%).

In the ongoing second cohort, which had received a PD-1 or PD-L1 therapy while being platinum chemotherapy naïve and cisplatin ineligible, investigators reported an ORR of 51% (95% CI, 40.8%-62.4%), including a confirmed CR rate of 20.0% and a confirmed PR rate of 31.0%. The median time to response was 1.8 months (interquartile range, 1.7-1.9) and the median DOR at 11 months was 10.9 months. Lastly, investigators reported a median PFS of 5.8 months (95% CI, 5.0-8.3) and a median OS of 14.7 months (95% CI, 10.5-18.2).

The agent was most recently examined in the phase 1b EV-103 trial (NCT02091999), which treated patients with locally advanced UC or mUC with a first-line combination of pembrolizumab and enfortumab vedotin.\(^{11} \) The combination regimen achieved a confirmed ORR of 73.4% (95% CI, 58.1%-85.4%); the CR rate was 15.6% and the PR rate was 57.8%.

Additionally, 93% of patients experienced reduction of tumor size from baseline. A median PFS of 12.3 months (95% CI, 7.98-NE) and a 12-month PFS rate of 50.1% were noted by investigators. The median OS was not reached and a 12-month OS rate of 81.6% (95% CI, 62.0%-91.8%) was observed. After a median follow-up of 10.4 months, the median DOR had not been reached and a 12-month DOR rate of 53.7% was observed (range, 1.2-12.9 months).

Lastly, sacituzumab govitecan was given an accelerated approval in April based on the results of the phase 2 TROPHU-U-01 trial (NCT03547973) for adult patients with locally advanced UC or mUC who had received a prior PD-1/PD-L1 inhibitor as well as a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.\(^{14} \) The decision was based on efficacy results from 112 patients in which the objective response rate was 27.7% (95% CI, 19.6%-36.9%), with 5.4% of patients having a CR and 22.3% having a PR. The median DOR was 7.2 months (95% CI, 4.7-8.6; range, 1.4-13.7).

For a full list of references, see the article at OncLive.com.

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**TABLE. ODAC Snapshot**

FDA review of accelerated approvals in mUC

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**ODAC, Oncologic Drugs Advisory Committee.**

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(Revised: May 18, 2017; Approved: April 17, 2017)
Physician Confidence in Biosimilars Rests on Real-world Data

by TONY HAGEN

PROVIDERS AND HEALTH CARE

Institutions want more real-world data on how patients respond to various biosimilar products, according to a varied panel of private practice, academic hospital, and group purchasing organization experts in a discussion at the Community Oncology Alliance virtual 2021 Community Oncology Conference in April.

More evidence is the tool for persuading oncology providers to switch to biosimilars, said E. Randolph “Randy” Broun, MD, a blood and marrow transplant specialist with Oncology Hematology Care (OHC), in Cincinnati, Ohio.

“Data are really lacking in this area,” Broun said. “Physicians are going to want data to understand that these truly are biosimilars that are interchangeable, and they’re not shortchanging their patients by doing this, even under pressure from payers.”

At Broun’s practice, biosimilars are a concept that physicians are very familiar with, and they use these agents in many settings. But their confidence in biosimilars can be strained when multiple versions of a single reference product start to appear and they are tasked with making the right choices for their patients.

“Once we have so many Herceptins [trastuzumab], are they all the same? Is it reasonable to simply pull a different one off the shelf for a patient who got something different 3 months ago? That will be a barrier. And you’re only going to solve that with a lot of data that are very convincing that these things are perfectly interchangeable,” Broun said.

According to Sandeep Parsad, PharmD, MBA, BCOP, assistant director of pharmacy at University of Chicago Medicine (UCM) in Illinois, her institution took a very purposeful approach to meet with physicians and nursing staff to talk about the regulatory requirements for approval and demonstrate how biosimilars were comparable with reference products and how they had a high standard for safety and quality.

When it approves a biosimilar, the FDA certifies that it is as safe and effective as the original biologic and that it has been rigorously evaluated. But the FDA does not give it automatic interchangeable status, meaning pharmacists would be free to substitute the biosimilar with a reference product without informing the physician.

“What I’ve heard [from our providers] as well as from other colleagues around the country is physicians prefer to be informed when there is a decision [about] whether or not we should switch from the reference product to the biosimilar,” Parsad said. “But I feel like...”
it went fairly smoothly once there was this very open dialogue.”

It was more of a challenge to develop policies about switching from reference products to biosimilars and in what instances this should occur. Many issues arose, such as whether patients should be asked for consent again before they are prescribed a biosimilar after being on a reference product or if a patient’s condition only carry the innovator products, Okon said. Accord- ing to Broun, at OHC, providers are now using biosimilars in nearly all situations when it comes to trastuzumab and rituximab and supportive care products, such as growth factors for the control

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Oncology Biosimilar Market Is Growing

**MORE BIOSIMILARS CONTINUE TO** be prescribed, and price competition is improving. Although the United States is behind Europe in terms of biosimilars approved and launched, the FDA is adding more approvals each year—29 since 2014—and 73 additional biosimilar candidates are in clinical trials and/or under FDA review.

In the hospital community, financial incentives are heavily weighted in favor of biologic reference products, which means that biosimilars in many cases are not even considered, said Ted Okon, MBA, executive director of the Community Oncology Alliance. He quoted from a January 2021 report from Bernstein Financial Advisory, which used a recent federal drug price disclosure mandate to probe what insurers are paying hospitals for the use of reference biologics.

For example, UT Southwestern Medical Center receives $17,241 from Cigna for administering a dose of the Neulasta originator brand of denosumab, whereas Aetna pays UT Southwestern $6474 per dose. Humana pays Wake Forest Baptist Medical Center $4370 for a dose of the Prolia originator brand of denosumab, whereas UnitedHealthcare pays Wake Forest $2209, according to the Bernstein report. As these data show, because compensation levels can sometimes be high, 30% to 43% of hospitals only carry the innovator products, Okon said.

Okon said the average markups over average selling prices on biologics are 250%. However, markups are often much higher, as indicated by the Bernstein information, especially if the drugs are acquired through the 340B Drug Pricing Program, which is intended to improve access to drugs for patients. Providing a scenario, Okon said it’s possible for a hospital to be paid almost $8000 for a drug whose wholesale cost is $4500, with the payer being charged over $8000 and the patient paying over $2000 out of pocket.

“You can see, especially with 340B, it makes drugs very, very economically attractive, and as a result, biosimilars are not attractive to use,” he said.

Citing information from IOVIA, Okon said the US market for biosimilars stands at $4 billion annually. Growth trajectories for filgrastim biosimilars have been slow but market share growth curves for more recent biosimilars for other products, including bevacizumab, trastuzumab, epoetin, and rituximab, have been very steep, Okon noted. Similarly, price declines due to biosimilar competition are becoming steeper, too.

Drivers holding back the growth of biosimilars include patent battles and restrictive deals that favor innovator products. Okon said pharmacy benefit managers and payers are responsible for the latter. Misconceptions about biosimilars are numerous. These include:

- Patients don’t want to take them
- Physicians don’t know about them
- Physicians won’t prescribe them because they’re not as efficacious as originator products
- Biosimilar naming suffixes and CMS coding for them are stifling growth
- Biologics are “natural monopolies” that shut out biosimilars

To improve access and lower prices, Okon suggested the FDA prioritize and streamline the approval process for biosimilars. He also said that rebate waivers for biologics should be eliminated and 340B drug discounts should be passed along to patients.

“The bottom line is this: the biosimilar market in the United States is growing and it’s producing savings,” Okon said. “But the solution is not price regulating the market. That will destroy not only the biosimilars but also the biologics market.”

This is an excerpt of a story that appeared in Centers for Biosimilars®. To read the full article, visit bit.ly/2QMKX07.
Expert Offers Advice on Saving for Retirement

by JEFF BENDIX


Q Please explain some of the savings tools available and their advantages and drawbacks.

A I think the most powerful way to save is always through retirement plans. People can put away money pretax, which means the government essentially is loaning them the money they would have paid in taxes. It’s asset-protected and tax-deferred. Also, many people don’t realize when they take the money out of these funds at retirement, it’s often taxed much lower than during their high-earning years.

We should always maximize retirement plan contributions. And for doctors in independent practice, we look to design more aggressive retirement plan savings. We add what are called defined benefit plans to their standard 401(k)s and try to maximize their pre-tax savings.

Q Please explain the difference between a defined benefit plan and a defined contribution.

A Defined contribution is a 401k or an individual retirement account (IRA), where the contribution is defined, but the investor doesn’t know what the benefit will be because it’s a function of how long they have participated in the IRA and how well the investments do.

A defined benefit plan is the opposite. Say a 50-year-old doctor decides to retire at age 65, and they would like to have a benefit of $150,000 per year for life. A pension company will tell the doctor lump sum they will need to have at 65 that could buy an annuity of $150,000 per year, and how much they’ll have to put in for the next 15 years to reach that lump sum. The benefit is defined.

If an individual’s debt is high interest, we’ll look to refinance or start an aggressive payoff for them. We’ll also suggest that a home mortgage be paid off by the time they’re entering that final phase in their career, or certainly by the time they retire.

Q At what point should a doctor start asking how much they’ll need in order to retire? And how do they calculate that number?

A There’s a broad consensus in the financial planning world that individuals can take 4% from a portfolio every year, adjusted for inflation, and it’s almost certain that they can go at least 30 years under even the worst-case scenario without running out of money.

We can come up with rough numbers based on what people want to spend and when they plan to stop earning an income. But we also make adjustments when they’re in the distribution years based on how much they’re actually spending and how much their investments are earning.

Q What do terms such as fee-only, fiduciary, and broker-dealer mean?

A Fiduciary means we put the client’s interest first. There’s a fiduciary oath where we basically say “I’m never going to do something that’s not in the client’s interest first.” For example, if we are investing a client’s money in a stock fund, we will use the lowest-cost one because you’re not getting a commission for using it. Fee-only means the only money the planner gets comes from the client. There’s no incentive to sell something. A lot of planners say they’re fee-based and that’s a disingenuous term because it means they can charge individuals a fee and take a commission.

The best places to find fiduciary fee-only advisors are the National Association of Personal Financial Advisors and a group of young fiduciary planners called the XY Planning Network.

This is an excerpt of a story that appeared in Medical Economics®. To read the full article, visit bit.ly/33EYFWw.
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Smoking Cessation Support Plays a Vital Role in Improving Lung Cancer Screening

by MATTHEW A. STELIGA, MD

RESULTS OF THE NATIONAL LUNG Screening Trial (NLST) demonstrated a 20% decrease in lung cancer mortality in individuals aged 55 to 74 years with a 30 pack-year smoking history using a low-dose computed tomography scan (LDCT). These data marked a turning point that led to the development of LDCT screening programs throughout the world. Many individuals undergoing screening are current smokers, which puts them at additional risk of developing a host of other diseases, so cessation at any point is beneficial.

Counseling and pharmacotherapy are effective evidence-based strategies, but many current smokers do not receive this support. We must recognize that the overarching goal of any cancer screening program is not merely to diagnose more cases or deliver more treatment but, ultimately, to help patients live longer, better lives.

SMOKING IN THE SCREENED POPULATION

The incidence of lung cancer even in this high-risk group undergoing screening is typically less than 2%. An overlooked and undertreated risk factor in patients undergoing screening for lung cancer is the very same one that makes them eligible for screening—smoking. Baseline demographics in the NLST indicated that 48.1% (n = 26,722) were current smokers at the time of enrollment.

Data from the University of Arkansas demonstrated that 70.2% (n = 309/440) of individuals undergoing LDCT were current smokers. Data have demonstrated that screen-detected abnormal LDCT findings were associated with increased cessation rates and, importantly, that normal scans were not associated with increased smoking or relapse in individuals who had quit.

In summary, the screened group evaluated for lung cancer may have a relatively low incidence of lung cancer, but often patients present with treatable conditions that are otherwise not optimally addressed.

BENEFITS OF CESSATION

Tobacco cessation may be viewed by many with the nihilistic perspective that "quitting now won’t make any difference" or "those individuals don’t want to quit." In actuality, most individuals who smoke do want to quit, and quitting at any point has significant benefits, especially following a diagnosis of cancer.

In findings from NLST, 24.1% (n = 930/3856) died of lung cancer. Interestingly, more individuals died because of cardiovascular disease (24.8%; n = 956/3856). In addition, 22.3% died because of other neoplasms, and 10.4% died of respiratory illnesses.

The majority of the deaths in NLST were because of tobacco-related diseases, with lung cancer representing less than a quarter of the overall deaths. We know that quitting smoking decreases cardiovascular risk, cerebrovascular events, and respiratory diseases; thus, if we wish to affect mortality rates through LDCT programs, detection and treatment of lung cancer are only part of the solution.

The National Comprehensive Cancer Network guidelines for lung cancer screening recommend that all current smokers be advised to quit. The degree to which individual programs advise patients can range widely. At minimum, patients may receive a verbal recommendation, print material, or a phone number for a quit-line.

A Cochrane review of smoking cessation concluded that a recommendation from a physician alone can increase cessation an additional 1% to 3%. Although physician advice does boost rates of quitting over offering no advice, there is room for improvement—and a structured program with counseling support and pharmacotherapy could potentially raise this rate several fold.

MAINSTAYS OF CESSATION

The details of evidence-based cessation support cannot be thoroughly covered in a brief perspective, but 2 broad categories include counseling and pharmacotherapy.

Counseling may include telephone counseling in the form of a quit-line, online counseling, group counseling programs, and individual counseling. Pharmacotherapy consists of nicotine replacement therapy, varenicline, or bupropion. More in-depth discussion of this is highlighted in other works. Much as we do not have the space to detail nuances of how to counsel patients, leaders overseeing lung screening programs do not have adequate time or expertise to counsel patients and deliver cessation support. This reinforces the criticality of having those in the LDCT workflow capable of providing this effective support.
The program at Winthrop P. Rockefeller Cancer Institute at University of Arkansas for Medical Sciences is run by an advanced practice registered nurse (APRN) who coordinates a team of APRNs and others with a background in tobacco cessation. The arrangements for the scan, follow-up calls for the results, and future contact are carried out by a member of our lung cancer team who is equipped with skills and time to provide counseling for cessation.

As we built and grew our program, cessation counseling was always a part of the care delivered, and the integration facilitated delivery.

OPT-OUT STRATEGY
Different programs have varying types of support, but regardless of the method, efficacy requires acceptance by the patient. Our early experience9 involved offering each patient an opportunity to visit with a counselor. By framing the visit as a choice, many patients declined.

Reframing cessation as an opt-out strategy led to presenting the patient with a message such as: “While you are here, we’re going to discuss smoking as a standard part of our program.” This shift led to most patients meeting with counselors face to face. Cancer Care Ontario demonstrated that structuring its smoking cessation program as an opt-out model led to 88% of individuals being offered a baseline LDCT attending a hospital-based counseling session.10

Regardless of the cessation resources used in a screening program, an opt-out strategy will likely have greater acceptance to patients and greater efficacy.

CONCLUSIONS
Lung cancer screening programs contain a high proportion of patients with a heavy smoking history who are unable to quit but may be receptive to support during this teachable moment. For example, if an LDCT program has a participation with a 50% smoking rate among individuals enrolled, consider that unaided cessation is approximately 2%. Rates for those individuals who receive cessation support with the addition of programs such as intensive telephone counseling and nicotine replacement therapy is approximately 20%, therefore it is reasonable to expect that the number of patients helped with smoking cessation could easily eclipse the number diagnosed and treated for cancer.11

Overall, smoking cessation may broaden the effect of lung cancer screening programs well beyond end points of cancer diagnosis and cancer mortality rates—helping even more of our patients lead longer, healthier lives. ■

REFERENCES

FIGURE. Hallmarks of Smoking Cessation

Smoking cessation resources vary and will vary in their efficacy depending on the individual. The availability of smoking cessation tactics, especially in conjunction with lung cancer screening programs, can have significant health benefits and decreased mortality, which extend beyond cancer incidence and cancer mortality.

FRAMEWORK FOR CESSTATION

“5 As”

1. Ask
2. Advise
3. Assess
4. Assist
5. Arrange

Counseling
Quit-lines
Sponsored programs
Individual sessions

Pharmacotherapy/Nicotine replacement therapy
Transdermal patch
Nasal spray/inhaler
Antidepressants

Electronic cigarettes
An alternative to nicotine replacement therapy, but not preferred
Guideline Update

NCCN Guidelines Include an Abundance of Options Across Myeloma Paradigm

by JESSICA HERGERT

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) guidelines for the management of frontline and relapsed/refractory multiple myeloma were updated to incorporate novel agents and combination strategies, providing a wide range of category 1 recommended therapies for patients, said Shaji K. Kumar, MD, during the 2021 NCCN Virtual Annual Conference.1

“The treatment paradigm of multiple myeloma continues to evolve at a rapid pace with the introduction of several new therapies and changing concepts in terms of treatment goals of this chronic disease,” said Kumar, a consultant for the Division of Hematology and a professor of medicine at Mayo Clinic. “The long list of different drugs and combinations that we can use underscores the progress that we have made in this field.”

Despite a wide range of systemic options, autologous stem cell transplant remains a key part of frontline treatment for eligible patients with newly diagnosed multiple myeloma, Kumar said. Updated findings from the IFM 2009 study showed that at a median follow-up of 93 months, the median progression-free survival (PFS) was 47.3 months with transplant after induction with the combination of bortezomib (Velcade), lenalidomide (Revlimid) and dexamethasone (VRd) vs 35.0 months with VRd alone (HR, 0.70; 95% CI, 0.59-0.92; 1-sided P = .0001).2

“Even with an effective induction therapy such as VRd, transplant still has a role to play,” Kumar said.

In the transplant-eligible setting, VRd remains the frontline standard of care for patients with newly diagnosed multiple myeloma and is included in the NCCN guidelines as a category 1 recommendation.1

Findings from the SWOG S0777 study demonstrated an overall response rate (ORR) of 81.5% with VRd vs 71.5% with lenalidomide plus dexamethasone (Rd) alone in this patient population.3 The median PFS was 43 months with VRd vs 30 months with Rd (1-sided P = .0018). The median overall survival (OS) was 75 months vs 64 months, respectively (2-sided P = .0250).

Updated data from the study demonstrated a median PFS of 41 months with VRd vs 29 months with Rd at a median follow-up of 84 months (HR, 0.74; 96% Wald CI, 0.59-0.93; 1-sided P = .003).4 The median OS was not reached with VRd compared with 69 months with Rd (HR, 0.70; 96% Wald CI, 0.54-0.93; 2-sided P = .0114).

Attempts have been made to improve upon the VRd regimen, Kumar said. For example, the phase 3 ENDURANCE trial swapped bortezomib for carfilzomib (Kyprolis; KRd); however, the data failed to demonstrate an improvement in PFS with KRd vs VRd in patients with newly diagnosed multiple myeloma.5 In addition, the carfilzomib-based regimen induced additional toxicity.

“The [ENDURANCE] trial included only standard-risk patients and also deferred stem cell transplant to the time of first relapse in those patients who were eligible to go to stem cell transplant,” said Kumar. “Nevertheless, it is important to note that, as a result of this trial, we still consider VRd the standard initial therapy for these patients.”

Despite these findings, KRd is a recommended regimen per the NCCN guidelines.1 Although quadruplet regimens are not yet commonly utilized as induction therapy in the United States, the combination of daratumumab (Darzalex), bortezomib, thalidomide (Thalomid), and dexamethasone is included as a useful regimen in certain circumstances in the NCCN guidelines.

“Given that thalidomide-based triplets are not common induction therapies in the US, the results of the GRIFFIN trial are more pertinent,” Kumar said.

The randomized phase 2 GRIFFIN trial demonstrated a 42.4% stringent complete response (sCR) rate with the combination of daratumumab and VRd vs 32.0% with VRd alone (odds ratio, 1.57; 95% CI, 0.87-2.82; P = .068).4 Long-term data for PFS are pending.

“There are certain settings, such as a high-risk patient population, where a quadruplet might be more appropriate given that these regimens are associated with higher minimal residual disease negativity, a characteristic that often appears to improve the outcomes of high-risk patients,” said Kumar.

“[However], while we are awaiting more data with [daratumumab and VRd], the standard approach is still thought to be a triplet containing a proteasome inhibitor [PI] and an immunomodulatory drug [IMiD] in the
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Joseph Mikhael, MD, MEd, FRCPC, FACP
Professor, Applied Cancer Research and Drug Discovery, Translational Genomics Research Institute (TGen)
City of Hope Cancer Center
Chief Medical Officer, International Myeloma Foundation

Saad Usmani, MD
Division Chief, Plasma Cell Disorders
Levine Cancer Institute – Atrium Health
transplant-eligible setting,” added Kumar. Additionally, the guidelines indicate that lenalidomide is a category 1 preferred maintenance regimen. Recommended maintenance options include ixazomib (Ninlaro) and bortezomib, with the combination of bortezomib and lenalidomide being a maintenance option in certain circumstances.

In the transplant-eligible setting, category 1 preferred regimens include ixazomib, daratumumab plus lenalidomide and dexamethasone, and lenalidomide plus low-dose dexamethasone per the NCCN guidelines.

The phase 3 ALCYONE trial demonstrated improved PFS, depth of response, and OS with daratumumab plus bortezomib, melphalan, and prednisone; however, similar OS with daratumumab plus bortezomib, stratumumab versus bortezomib, melphalan, and dexamethasone alone. Updated findings demonstrated improved PFS, depth of response, PRs in patients who had received a median 47.9 months, the median OS was 9 months with the doublet (HR, 0.54; 95% CI, 0.43-0.67; P = .0001). Additionally, the phase 3 TOURMALINE MM2 trial demonstrated a median PFS of 35.3 with oral ixazomib plus lenalidomide and dexamethasone vs 21.8 months with placebo plus lenalidomide and dexamethasone in patients with transplant-eligible, newly diagnosed multiple myeloma (HR, 0.83; 95% CI, 0.67-1.018; P = .073). Although the trend for PFS was positive with the triplet, these results were not statistically significant.

Daratumumab plus lenalidomide and dexamethasone is included in the guidelines as a category 1 preferred regimen, but ixazomib plus lenalidomide and dexamethasone is also included as a recommended regimen.

As in the frontline setting, the armamentarium of relapsed/refractory multiple myeloma is rich with preferred and recommended triplet regimens per the NCCN guidelines.

For example, bortezomib in combination with daratumumab and dexamethasone is a recommended option, as is pomalidomide (Pomalyst) plus dexamethasone. Lenalidomide-based triplets, such as lenalidomide plus carfilzomib and dexamethasone, lenalidomide plus daratumumab and dexamethasone, and lenalidomide plus ixazomib and dexamethasone, are also category 1 preferred regimens.

“All of these 3-drug combinations have led to an improvement in PFS and, in some cases, improved OS as well [compared with the control regimens],” said Kumar.

However, many patients with early relapsed multiple myeloma are refractory to lenalidomide, having received it as frontline induction or maintenance therapy, Kumar added.

As such, the phase 3 ICARIA-MM trial randomized patients with relapsed/refractory multiple myeloma to isatuximab-irfc (Sarclisa) plus pomalidomide and dexamethasone or pomalidomide plus dexamethasone alone. At a median follow-up of 11.6 months, the median PFS was 11.53 months with the triplet vs 6.47 months with the doublet (HR, 0.596; 95% CI, 0.436-0.814; P = .001). Similarly, the phase 3 APOLLO trial randomized patients who had received at least 1 line of prior therapy, including lenalidomide and a PI, to receive daratumumab plus pomalidomide and dexamethasone or pomalidomide plus dexamethasone alone. At a median follow-up of 16.9 months, the median PFS with the triplet was 14.7 months vs 6.9 months with the doublet (HR, 0.63; 95% CI, 0.47-0.85; P = .003).

Additionally, the phase 3 CANDOR trial after a median follow-up of 8.6 months, the median OS was 8.6 months with the doublet (HR, 0.63; 95% CI, 0.47-0.85; P = .003).

The combination of carfilzomib, dexamethasone, and daratumumab (KdD) demonstrated efficacy in this patient population in the phase 3 CANDOR trial. After a median follow-up of approximately 17 months, the median PFS was not reached with KdD vs 15.8 months with carfilzomib/dexamethasone alone (HR, 0.63; 95% CI, 0.46-0.85; P = .0027). Additionally, interim findings from the phase 3 IKEMA trial showed that the median PFS was not reached with the combination of isatuximab, carfilzomib, and dexamethasone vs 19.15 months with carfilzomib/dexamethasone (HR, 0.531; 99% CI, 0.318-0.889; P = .0007).

“The IKEMA study results” suggested that a monoclonal antibody in combination with a next-generation PI would be quite an appropriate choice for someone who is relapsing on lenalidomide maintenance treatment,” Kumar said.

In the setting of late-relapsed, heavily pretreated multiple myeloma, novel agents, such as selinexor (Xpovio) and belantamab mafodotin-blmf (Blenrep), are also listed as recommended treatment options.

Initially, in the phase 2 STORM trial, selinexor in combination with dexamethasone demonstrated an ORR of 26.2%, including 2 sCRs in patients who had received a median of 7 prior lines of treatment for multiple myeloma. The median duration of response was 4.4 months, the median PFS was 3.7 months, and the median OS was 8.6 months with selinexor plus dexamethasone.

Building on these results, the phase 3 BOSTON trial randomized patients with relapsed/refractory myeloma who received 1 to 3 prior lines of therapy to once-weekly selinexor plus bortezomib and dexamethasone or twice-weekly bortezomib plus dexamethasone. The median PFS was 13.93 months with the triplet vs 9.46 months with the doublet (HR, 0.70; 95% CI, 0.53-0.93; P = .0075).

As such, the once-weekly triplet regimen is now included as a category 1 recommended regimen, whereas other selinexor-based regimens, such as selinexor plus dexamethasone, selinexor plus daratumumab and dexamethasone, and selinexor plus pomalidomide and dexamethasone, may be useful in certain circumstances.
Larotrectinib Achieves High Marks in NTRK-Mutant Thyroid Cancer

by KYLE DOHERTY

LAROTRENTINIB (VITRAKVI) HAS proved to be highly active in patients with thyroid cancer with NTRK gene fusions, exhibiting rapid and durable disease control, according to Maria E. Cabanillas, MD.

Cabanillas, professor of clinical research in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas MD Anderson Cancer Center in Houston, pooled and analyzed larotrectinib therapy outcomes in a subset of patients with thyroid cancer harboring an NTRK gene fusion from a phase 1 trial (NCT02122913) and the phase 2 NAVIGATE trial (NCT02576431) as part of an OncLive® Rapid Readout program. The video series features experts exploring key findings presented at conferences. The analysis was originally presented at the European Society for Medical Oncology Virtual Congress 2020.

“NTRK gene fusions encode chimeric TRK [tropomyosin receptor kinase] proteins, which are constitutively active and act as oncogenic drivers in a wide variety of adult and pediatric solid tumors,” Cabanillas explained. “Larotrectinib [previously] demonstrated a 79% overall response rate and a 35.2-month duration of response in patients with TRK fusion cancer, regardless of tumor type or age.”

A total of 28 patients were included in the analysis: 4 adult patients from the phase 1 trial (NCT02122913) and the phase 2 NAVIGATE trial (NCT02576431) as part of an OncLive® Rapid Readout program. The video series features experts exploring key findings presented at conferences. The analysis was

The primary end point of the analysis was best objective response rate (ORR) per investigator assessment via RECIST v1.1. Secondary end points included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Investigators reported that larotrectinib elicited an ORR of 75% (95% CI, 55%-89%), with 7% of patients experiencing a complete response (TABLE 1). The median time to response was 1.9 months (range, 1.6-5.6). Median OS was 27.8 months (95% CI, 16.7-not estimable [NE]); both the median PFS (95% CI, 14.8-NE) and median DOR (95% CI, 16.6-NE) were not reached. However, the DOR and PFS rates at 12 months were 95% (95% CI, 85%-100%) and 81% (95% CI, 67%-96%), respectively.

In 7 patients with anaplastic thyroid cancer, the ORR was 29% (95% CI, 4%-71%), which Cabanillas noted was a good result for this highly aggressive cancer type. Twenty-one patients with differentiated (papillary or follicular) thyroid cancer experienced
a higher ORR than the overall population (90%; 95% CI, 70%-99%). The 18-month PFS for patients with differentiated thyroid cancer was also an impressive 86% (95% CI, 66%-100%).

Larotrectinib is a first-in-class, selective, central nervous system (CNS)-active TRK inhibitor that specifically inhibits TRKA, TRKB, and TRKC. The FDA granted accelerated approval to the agent in November 2018 for adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation that are either metastatic or for which surgical resection is likely to result in severe morbidity and who have progressed following treatment or have no satisfactory alternative treatment.

**CLINICAL TRIAL DETAILS**
The phase 1 trial was a randomized, open-label trial that enrolled 75 adult patients with advanced solid tumors. Larotrectinib was administered orally as a capsule or liquid solution over continuous 28-day cycles in doses ranging from 50 mg to 200 mg, depending on tumor type. Patients with clinically significant cardiovascular disease or a history of myocardial infarction were excluded from the study, as well as those with an active, uncontrolled infection and those who were pregnant or lactating.

**NAVIGATE** was an open-label phase 2 study of 203 patients who were 12 years and older with NTRK fusion-positive tumors. Larotrectinib was administered orally as a capsule or liquid solution at a dose of 100 mg twice daily in continuing 28-day cycles. Patients excluded from the trial included those with prior progression while receiving approved or investigational tyrosine kinase inhibitors targeting TRK, those with symptomatic or unstable brain metastases, and those with an active, uncontrolled infection.

Patients with thyroid cancer enrolled in the trial had a median age of 61.5 years (range, 6-80), and 14% had CNS metastases. Nearly half (43%) had received no prior systemic therapies; 25% had received 1, 25% had 2, and 7% had 3 or more. Further, 43% of the population were patients with an NTRK1 gene fusion; the remaining 57% were patients with an NTRK3 fusion.

Commonly reported treatment-emergent adverse events in the analysis were mostly grade 1 or 2, and with the most frequently observed events being fatigue (36%), constipation (32%), and dizziness (32%). No patients experienced adverse events leading to permanent discontinuation of treatment.

**REFERENCES**

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**TABLE 1. Larotrectinib Efficacy Results From Pooled Analysis by Thyroid Cancer Subtype**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Differentiated (n = 21)</th>
<th>Anaplastic (n = 7)</th>
<th>Total population (n = 28)</th>
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<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>90% (70%-99%)</td>
<td>29% (4%-71%)</td>
<td>75% (55%-89%)</td>
</tr>
<tr>
<td>CR</td>
<td>10%</td>
<td>0%</td>
<td>7%</td>
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<tr>
<td>PR</td>
<td>81%</td>
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<tr>
<td>PD</td>
<td>0%</td>
<td>43%</td>
<td>11%</td>
</tr>
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</table>

CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

**TABLE 2. Common Treatment-Emergent Adverse Effects From NCT02122913 and NAVIGATE Trials**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fatigue</th>
<th>Constipation</th>
<th>Dizziness</th>
<th>Increased ALT</th>
<th>Anemia</th>
<th>Increased AST</th>
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</thead>
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<tr>
<td>1 or 2</td>
<td>36%</td>
<td>32%</td>
<td>29%</td>
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<td>14%</td>
<td>29%</td>
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<td>0%</td>
<td>4%</td>
<td>0%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<td>0%</td>
</tr>
<tr>
<td>Any grade</td>
<td>36%</td>
<td>32%</td>
<td>32%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase.
A NEW APPROACH IN 1L aRCC TREATMENT...

NOW APPROVED

CABOMETYX® (cabozantinib) tablets

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INDICATIONS
CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

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1L=first-line; aRCC=advanced renal cell carcinoma.
The first and only 1L aRCC combination treatment to double PFS and ORR while delivering superior OS\(^1\)

More than 16 months median PFS\(^1\)*

CheckMate-9ER was a randomized (1:1), open-label, phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.\(^2\)

*PFS and ORR were assessed by IRC.

**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS**

**Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea. Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

**Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Hepatotoxicity:** CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥4) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0–1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

**Adrenal Insufficiency:** CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab depending on severity. Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.3%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC. Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

**Proteinuria:** Proteinuria was observed in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive procedures. Advise patients who have received hormone replacement therapy, including systemic corticosteroids, to use effective contraception.

**Lactation:** CABOMETYX is excreted in breast milk. Advise women not to breastfeed during treatment.

**Embryo-Fetal Toxicity:** CABOMETYX can cause fetal harm. Women of reproductive potential should be advised of the potential risk to a fetus. Verify the pregnancy status of women of reproductive potential before initiating CABOMETYX.

**Informing Healthcare Providers**

Please see Brief Summary of the Prescribing Information or call 1-800-FDA-1088. You are encouraged to report negative side effects of CABOMETYX to the FDA MedWatch program at 1-800-FDA-1088 or at www.fda.gov/medwatch.
More than double ORR†‡

<table>
<thead>
<tr>
<th>CABOMETYX + OPDIVO (n=323)</th>
<th>sunitinib (n=328)</th>
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<tbody>
<tr>
<td>Patients (%)</td>
<td>ORR: P&lt;0.0001</td>
</tr>
<tr>
<td>55.7% (180/323)</td>
<td>27.1% (89/328)</td>
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<tr>
<td>48% CR</td>
<td>23% CR</td>
</tr>
<tr>
<td>8% PR</td>
<td>4.6% PR</td>
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</table>

5.6% of patients had progressive disease with CABOMETYX + OPDIVO vs 13.7% of patients with sunitinib‡

†PFS and ORR were assessed by BICR.

Superior OS outcomes¹

- 40% reduction in risk of death with CABOMETYX + OPDIVO (HR=0.60; 98.89% CI: 0.40-0.89; P=0.0010)¹
  - Median OS not reached in either treatment arm

New CABOMETYX combination starting dose

CABOMETYX 40 mg starting dose—optimized for combination treatment with OPDIVO¹

- CABOMETYX 40 mg once daily
- OPDIVO 240 mg every 2 weeks (30-minute IV infusion)
- OPDIVO 480 mg every 4 weeks (30-minute IV infusion)

IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS

periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

- CABOMETYX as a single agent: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.
- CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John’s wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

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

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>CA125 Level</th>
<th>EMA Level</th>
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Table 3. Laboratory Data

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Table 4. Adverse Events in Patients Receiving CA125 and Hemovasculature

<table>
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<tr>
<th>Event Type</th>
<th>CA125 Level</th>
<th>EMA Level</th>
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<td>10.1</td>
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</tr>
<tr>
<td>Platelet</td>
<td>11.2</td>
<td>11.2</td>
<td>11</td>
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<td>White Blood Cells</td>
<td>12.3</td>
<td>12.3</td>
<td>12</td>
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Next Generation of PDGFR Inhibitors Makes Headway in GIST

by JANE DE LARTIGUE, PhD

DYSREGULATED PLATELET-DERIVED growth factor receptor (PDGFR) signaling is implicated in a number of cancer types and is among the targets of many FDA-approved multikinase inhibitors. Despite the success of these drugs in a range of malignancies, it is difficult to know the contribution that PDGFR antagonism makes to their anticancer effects, particularly when other kinase targets, such as BCR-ABL and VEGFRs, have better-characterized roles in the pathophysiology of the cancer types for which these agents are approved.

The exception is gastrointestinal stromal tumors (GIST), in which PDGFR mutations are well-established drivers. Imatinib (Gleevec), which includes PDGFR among its targets, has been approved for the treatment of patients with KIT-positive unresectable or metastatic GIST. The payoff has been paradigm shifts in the treatment of patients with GIST in an effort to tackle resistance to imatinib. However, none of these drugs targeted PDGFR A842V, the most common PDGFR mutation observed in patients with GIST.

That all changed in January 2020 when avapritinib (Ayvakit) became the first drug approved for the treatment of D842V-mutant GIST, demonstrating unprecedented durable responses in this patient population. In May 2020, ripretinib (Ginlock), which also targets the PDGFR D842V mutation, gained FDA approval, ushering in a new generation of precision therapeutics for GIST.

PROMISCUITY PAYS OFF As prominent drivers of many of the hallmark capabilities of cancer that are readily druggable by small-molecule inhibitors, dysregulated kinases have been at the forefront of pharmaceutical research and development efforts in oncology for decades. The payoff has been paradigm shifts in the treatment landscapes for a range of cancers.

Although many potent, highly specific inhibitors of a single oncogenic kinase have been developed, the story began in 2001 with a multitargeted drug. Imatinib, initially approved for the treatment of patients with chronic myeloid leukemia (CML), was hailed as a “magic bullet” for cancer and paved the way for the many kinase inhibitors that followed in its wake.

Imatinib was developed as an inhibitor of the central oncogenic driver of CML, the BCR-ABL fusion protein, which results from a chromosomal rearrangement (dubbed the Philadelphia chromosome) that yields a fusion involving the ABL gene, which encodes a kinase. However, imatinib also was shown to have activity against a number of other kinases, including PDGFR.

Capitalizing on this promiscuous activity, imatinib has been approved in multiple cancer types, including several in which PDGFR plays an oncogenic role. Dermatofibrosarcoma protuberans (DFSP) is a rare type of cutaneous soft tissue sarcoma. More than 90% of DFSP cases are characterized by chromosomal rearrangements that result in the COL1A1 gene fused to the PDGFB gene.

Imatinib was approved by the FDA for the treatment of patients with DFSP in 2006 and, according to a recent systematic review, is associated with objective responses in more than 60% of advanced cases. Imatinib is also approved for the treatment of patients with chronic eosinophilic leukemia, which frequently displays a gene fusion between the FIP1L1 gene and the PDGFR gene.

The cancer type in which PDGFR has the most well-established role, however, is another rare form of sarcoma, GIST. The majority of GIST cases are defined by mutually exclusive gain-of-function mutations in either KIT or PDGFR, both of which lead to constitutive activation of these kinases and the same downstream signaling pathways.

Although KIT mutations dominate the genomic landscape of GIST, accounting for approximately 80% of cases, another 5% to 10% of patients harbor alterations in PDGFR (Figure). PDGFR mutations in GIST typically involve exon 12, 18, or, more rarely, 14, which encode the juxtamembrane domain, activation loop, and adenosine triphosphate (ATP)-binding domain, respectively. PDGFR-mutant GISTs often exhibit clinicopathologic differences from their KIT-mutant counterparts: they occur almost exclusively in the stomach, are more often epithelial in nature, and tend to be less aggressive.

In 2002, imatinib received accelerated approval for the treatment of patients with KIT (CD117)-positive advanced/metastatic GIST, followed in 2008 by accelerated approval for adjuvant use in patients with resected KIT-positive GIST. Imatinib remains standard of care in both settings.

Imatinib has transformed the treatment of patients with GIST, who previously would have received an extremely poor prognosis. The majority of patients with GIST...
The PDGFR Network

Growth Factor Signaling in Context

by JANE DE LARTIGUE, PhD

PLATELET-DERIVED GROWTH FACTOR RECEPTORS (PDGFRs) are typical tyrosine kinase receptors that span the cell membrane and contain several distinct domains. An extracellular domain composed of immunoglobulin-like domains functions as a binding site for activating ligands. On the inner side of the cell membrane is the tyrosine kinase domain, responsible for the catalytic activity of PDGFRs.1-3

There are 2 receptor isoforms, PDGFRα and PDGFRβ, which are encoded by the PDGF and PDGRβ genes, respectively. PDGFRα and PDGFRβ evoke similar downstream signaling cascades in the cell following binding by PDGF ligands. There are 4 known PDGF ligands—PDGF-A, -B, -C, and -D—but their biological activity requires the formation of dimers, with 4 possible resultant domains (PDGF-AB).1-3

Two additional multitargeted kinase inhibitors that address some of these resistance mutations have been approved for the treatment of patients with advanced/metastatic GIST. Sunitinib (Sutent) and regorafenib (Stivarga) have been authorized for second- and third-line treatment, respectively.20,21

Sunitinib and regorafenib also target VEGFRs, highlighting another function of FDA-approved multikinase inhibitors as antiangiogenic agents. Angiogenesis, the formation of new blood vessels from existing vasculature, is regulated by a delicate balance between pro- and antiangiogenic factors within the cell. Dysregulated angiogenic signaling pathways, which lead to aberrant vasculature, are a hallmark of cancer.22-24

Both VEGFR and PDGFR signaling pathways play important roles in angiogenesis.

FIGURE. Growth Factors and Receptors in Signaling Networks

Dysregulated platelet-derived growth factor receptors (PDGFrs) are among the tyrosine kinase receptors that can play a role in oncogenic signaling through several networks. Adapted under a Creative Commons license from Qin S et al. / Hematol Oncol. 2019;12(1):27. doi:10.1186/s13045-019-0718-5
A variety of multi-kinase inhibitors that target these receptors in addition to other kinases have proved effective against several cancer types, including highly vascularized tumors such as renal cell carcinoma and hepatocellular carcinoma. However, the contribution of PDGFR inhibition to their efficacy remains unclear.22-24

**THE NEXT GENERATION**

In the past 20 years, the FDA has approved at least 12 kinase inhibitors that include PDGFR among their targets for oncologic indications in hematologic and solid tumors (TABLE 1).25-28

The first drug that specifically targeted PDGFR to come to market was olaratumab (Lartruvo), which received accelerated approval from the FDA in 2016 for adult patients with certain subtypes of soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery. However, the indication was withdrawn in 2019 following a failed phase 3 trial.29-31

Ongoing clinical trials of kinase inhibitors that target PDGFR more specifically are being conducted in biomarker-selected and unselected populations. Although development of approved multi-kinase inhibitors is ongoing in a range of tumor types with other targets, a study involving dasatinib (Sprycel) in patients with gliomas with PDGF mutations is underway (NCT02847429). A new generation of PDGFR inhibitors is designed for the treatment of GIST, with the goal of blocking the activity of the D842V mutation. Imatinib, sunitinib, and regorafenib are all type II tyrosine kinase inhibitors; they bind to the inactive kinase and block its ability to become activated.1,33 As a type I inhibitor, avapritinib binds to the active conformation of the kinase. It

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### TABLE 1. FDA-Approved Kinase Inhibitors With Targets Including PDGFR

<table>
<thead>
<tr>
<th>Agent (brand name; developer)</th>
<th>Kinase targets</th>
<th>Tumor-type approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec; Novartis)</td>
<td>PDGFRα/β, BCR-ABL, KIT1</td>
<td>Ph-positive CML, ALL, HES, CEL, DFSP, KIT-positive GIST, MDS, MPD, ASM without KIT D816V mutation or mutational status unknown</td>
</tr>
<tr>
<td>Dasatinib (Sprycel; Bristol Myers Squibb)</td>
<td>PDGFRα/β, BCR-ABL, SRC, LCK, YES, FYN, KIT, EPHA2</td>
<td>Ph-positive CML, ALL</td>
</tr>
<tr>
<td>Nilotinib (Tasigna; Novartis)</td>
<td>PDGFRα/β, BCR-ABL, SRC, LCK, YES, FYN, KIT, EPHA2</td>
<td>Ph-positive CML</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>PDGFRα/β, BCR-ABL, SRC, LCK, YES, FYN, KIT, EPHA2</td>
<td>Ph-positive CML</td>
</tr>
<tr>
<td>Lenvatinib (Lenvima; Eisai Inc)</td>
<td>PDGFRα/β, VEGFR2, FGFR, KIT RET</td>
<td>DTc, RCC, HCC, endometrial carcinoma</td>
</tr>
<tr>
<td>Avapritinib (Ayvakit; Blueprint Medicines)</td>
<td>PDGFRα D842V, KIT D816V</td>
<td>PDGFRα-mutant GIST, including D842V</td>
</tr>
<tr>
<td>Ripretinib (Ginlock; Deciphera Pharmaceuticals)</td>
<td>Mutant PDGFRα, mutant KIT3</td>
<td>GIST</td>
</tr>
<tr>
<td>Sorafenib ( Nexavar; Bayer)</td>
<td>PDGFRα/β, BRAF, V600E, CRAF, KIT, FLT3, RET, VEGFR1/2/3</td>
<td>RCC, HCC, DTC</td>
</tr>
<tr>
<td>Sunitinib (Sutent; Pfizer)</td>
<td>PDGFRα/β, VEGFR1/2/3, KIT, FLT3, CSF1R, RET</td>
<td>RCC, GIST, pNETs</td>
</tr>
<tr>
<td>Pazopanib (Votrient; Novartis)</td>
<td>PDGFRα/β, VEGFR2, FGFR, KIT, CSF1R7</td>
<td>Soft tissue sarcoma, RCC</td>
</tr>
<tr>
<td>Regorafenib (Stivarga; Bayer)</td>
<td>PDGFRα, VEGFR2, FGFR, KIT, RET, RAF</td>
<td>CRC, HCC, GIST</td>
</tr>
<tr>
<td>Axitinib (Inlyta; Pfizer)</td>
<td>PDGFRα/β, VEGFR1/2/3</td>
<td>RCC</td>
</tr>
</tbody>
</table>

**TABLE 2. Select Studies of PDGF-Specific Trials and Inhibitors**

<table>
<thead>
<tr>
<th>Agent (brand name if applicable; industry developers)</th>
<th>Phase and clinical setting (trial name if applicable; ClinicalTrials.gov identifier)</th>
</tr>
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<tbody>
<tr>
<td>Dasatinib (Sprycel; Bristol Myers Squibb)</td>
<td>Phase 2—everolimus in pediatric/young adult gliomas with PDGFRα, PDGFRβ, PDGFA, PDGFB alterations (NCT03352427)</td>
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<tr>
<td>Axitinib</td>
<td>Phase 2—Advanced systemic mastocytosis (PATHFINDER; NCT03580655)</td>
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<tr>
<td>Avapritinib (Ayvakit; Blueprint Medicines)</td>
<td>Phase 1/2—Pediatric patients with KIT- or PDGFRα-mutant solid tumors (NCT04771520)</td>
</tr>
<tr>
<td>Ripretinib (Ginlock; Deciphera Pharmaceuticals)</td>
<td>Phase 3—vs placebo in advanced GIST (INIVITUS; NCT03353753)</td>
</tr>
<tr>
<td>Crenolanib (Arog Pharmaceuticals)</td>
<td>Phase 3—Advanced solid or hematologic malignancies (NCT02571036)</td>
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AML, acute myeloid leukemia; GIST, gastrointestinal stromal tumor; PDGF, platelet-derived growth factor; R/R, relapsed or refractory.

*Not yet recruiting participants.

bTrial is ongoing but no longer recruiting participants.

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AML, acute myeloid leukemia; GIST, gastrointestinal stromal tumor; PDGF, platelet-derived growth factor; R/R, relapsed or refractory.

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bTrial is ongoing but no longer recruiting participants.
has been shown to potently inhibit KIT and PDGFRA mutations, including activation loop mutations such as D842V. In January 2020, avapritinib became the first drug specifically approved for the treatment of patients with advanced/metastatic GIST with D842V and other PDGFRA exon 18 mutations.

Approval was based on the results of the multicenter, single-arm, open-label phase 1 NAVIGATOR study (NCT02508532). A total of 82 patients enrolled across the dose-escalation and dose-expansion portions of the trial, 56 of whom had the D842V mutation (20 in dose escalation and 36 in dose expansion). During dose escalation, patients received doses ranging from 30 to 600 mg; in the dose-expansion phase, patients initially received a dose of 400 mg, which was reduced to 300 mg after a review of initial data.

At a median follow-up of 15.9 months in the D842V population, the confirmed overall response rate (ORR) was 88%, and 9% of patients had a complete response. Common grade 1 or 2 treatment-related adverse events (TRAEs) at the 300-mg dose included nausea, diarrhea, decreased appetite, and fatigue. Across doses, grade 3 or 4 TRAEs occurred in 57% of patients, the most common of which was anemia.

Long-term follow-up results for this study’s D842V group were recently published. At a median follow-up of 27.5 months, median overall survival (OS) had not yet been reached. With a median PFS of 34 months and ORR of 91%, avapritinib showed clinical activity deemed “unprecedented” by the study investigators. Additionally, TRAEs continued to be manageable.

Meanwhile, the FDA denied a separate application for the approval of avapritinib for four-line treatment of patients with advanced/metastatic GIST. A complete response letter was issued after the phase 3 VOYAGER trial (NCT03465722), in which avapritinib was compared with regorafenib in patients with third- or fourth-line GIST regardless of tumor mutation status, failed to meet its primary end point of improved PFS. Median PFS was not significantly different between the 2 arms (4.2 months for avapritinib compared with 5.6 months for regorafenib).

Ripretinib also is designed to inhibit a spectrum of KIT and PDGFRA mutations, including D842V, but with a mechanism of action distinct from that of avapritinib. Similar to imatinib, ripretinib is a type II inhibitor; it binds to the activation loop and locks PDGFR in an inactive conformation. However, ripretinib also binds to a “switch pocket” located in the ATP-binding domain, preventing it from interacting with the activation loop and thus providing an extra means of dampening kinase activity.

The FDA approved ripretinib in May 2020 for fourth-line treatment of advanced/metastatic GIST, based on the results of the phase 3 INVICTUS trial (NCT03353753), in which patients (N = 129) were randomized to receive either ripretinib or placebo. Ripretinib led to a significant improvement in median PFS (6.3 months compared with 1.0 month for placebo [HR, 0.15; 95% CI, 0.15-0.62]). Median OS was 15.1 months in the ripretinib arm compared with 6.6 months in the placebo arm (HR, 0.36; 95% CI, 0.21-0.62). However, due to the trial’s hierarchical testing of end points, the nonsignificant ORR meant that statistical significance of the OS data could not be formally tested. The most common TRAEs included alopecia, myalgia, nausea, fatigue, hand-foot syndrome, and diarrhea. Grade 3/4 TRAEs included increased lipase, hypertension, fatigue, and hypophosphatemia.

Ripretinib is being compared with sunitinib as a second-line treatment option in the phase 3 INTRIGUE trial (NCT03673501), which has completed enrollment; top-line data are expected in the second half of 2021.

Finally, crenolanib is a highly selective inhibitor of PDGFR and FLT3 that impedes both the wild-type and mutant forms of these 2 proteins, including the PDGFRA D842V mutation. It previously demonstrated a clinical benefit rate of 31% in a phase 1/2 trial in patients with advanced/metastatic PDGFRA D842V-mutated GIST (NCT01243346), with in vitro activity against PDGFRA D842V (cellular IC50 9 nM), which prompted an ongoing phase 3 clinical trial in this patient population (NCT02847429).
New DLBCL Treatments Are Poised to Fill an Unmet Need for Patients in Challenging Settings

by CHRISTINA T. LOGUIDICE

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) is a fast-growing, aggressive disease, but it is often curable with timely and appropriate treatment. Nevertheless, approximately 25% to 33% of patients have primary refractory disease or relapse, both of which are associated with worse outcomes.1,2 Although a curative approach may still be possible for some of these patients, the treatments required may be contraindicated in others. Recently, several effective second- and subsequent-line treatments have emerged for the population of patients who are not candidates for the intensive treatments considered necessary for cure, such as consolidation with high-dose therapy.

During a recent OncLive Peer Exchange®, a panel of lymphoma experts discussed these therapies, including tafasitamab-cxix (Monjuvi), polatuzumab vedotin-piiq (Polivy), and selinexor (Xpovio), and how and when they use them for their patients.

“The toxicities associated with our traditional regimens have been so great,” said Loretta J. Nastoupil, MD. “There’s probably a large number of patients who are having fewer of these intensive approaches because we make the determination that they’re not going to tolerate it.” Nastoupil noted that the newly available treatments give patients the opportunity for more effective and tolerable palliation, often with durable results.

TAFASITAMAB

On July 31, 2020, the FDA granted accelerated approval to tafasitamab in combination with lenalidomide (Revlimid) for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low-grade lymphoma, who are not candidates for autologous stem cell transplant.3 “Tafasitamab is a CD19 antibody,” Kami J. Maddocks, MD, said. She explained that it was initially studied as a single agent in a phase 2 study where it showed some durable complete responses, which then served as the rationale for combining it with lenalidomide.

Approval of tafasitamab in combination with lenalidomide was based on data from L-MIND (NCT02399085), an open-label, multicenter, single-arm, phase 2 trial that included 80 patients who received at least 1 dose of both tafasitamab and lenalidomide.4 “The first 3 months [of treatment] were pretty aggressive. They were treated with weekly infusions, then they were treated bimonthly. After a year, patients were able to go on to maintenance therapy with the antibody tafasitamab alone if they were responding,” Maddocks said.

After a median follow-up of 13.2 months, 48 patients (60%) had an objective response.
of which 34 (42.5%) were complete responses (CRs) and 14 (17.5%) were partial responses (PRs). These findings were confirmed after more than 2 years of follow-up, with 47 patients (58.8%) having an objective response, with 33 (41.3%) being CRs and 14 (17.5%) being PRs. Additionally, 12 patients (15%) had stable disease. Responses were durable, with a median duration of response of 34.6 months. The median overall survival (OS) was 31.6 months with a median follow-up of 31.8 months, and the median IRC-assessed duration of response greater than 24 months (range, 26.6–38.6 months) at last follow-up, with 25 patients who achieved PRs or CRs to the polatuzumab vedotin combination, responses lasted at least 6 months in 16 patients (64%) and at least 12 months in 12 patients (48%).

Benefit with the addition of polatuzumab vedotin to bendamustine/rituximab continued to be observed after a median follow-up of almost 43 months. In the polatuzumab vedotin combination arm, 6 patients (15%) had an independent review committee (IRC)-assessed duration of response greater than 24 months (range, 26.6–38.6 months) at last follow-up, with 5 receiving no new treatment and 1 undergoing an allogeneic stem cell transplant. The median IRC-assessed PFS was 9.2 months in the polatuzumab vedotin combination arm vs 3.7 months in the bendamustine/rituximab arm, whereas the median OS was 12.4 months vs 4.7 months, respectively.

The most common TEAEs in the polatuzumab vedotin arm included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia. Serious TEAEs were reported in 64% of patients, most frequently from infection, with the most common reason for treatment discontinuation being cytopenia (18% of all patients). No new safety signals were observed during the longer follow-up period.

“The FDA approval for this combination is for treatment in the third-line setting or beyond...[but] I've used it as either second- or third-line therapy,” Burke said. He explained that in a subset analysis the patients who received it in the second line had better outcomes than those receiving it in the third line and beyond, and that he has not had any trouble getting the regimen covered by insurance in these settings.

Burke also noted that he has used polatuzumab vedotin before CAR T-cell therapy. Moderator Ian W. Finn, MD, PhD, agreed with that approach, adding that “it's attractive as a bridging therapy for patients who require it,” but said he worries about using a T cell–depleting agent prior to a patient acquiring the leukapheresis product. However, he said he has been

<table>
<thead>
<tr>
<th>TABLE 1. TEAEs Per Patient Year of Exposure to L-MIND Treatment Regimen</th>
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</thead>
<tbody>
<tr>
<td><strong>Most frequent ≥ grade 3 TEAE</strong></td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>1.14</td>
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<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>0.26</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>0.11</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>0.07</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>0.06</td>
</tr>
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<td><strong>TEAE, treatment-emergent adverse effect</strong></td>
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</table>

introducing tafasitamab prior to CD19-directed CAR T-cell therapy is going to impact [the curative potential of the CAR T-cell therapy],” Nastoupil said, indicating that more real-world experience is needed to gain a better sense of how to optimally sequence available treatments.

**POLATUZUMAB VEDOTIN**

On June 10, 2019, the FDA approved polatuzumab vedotin in combination with bendamustine and rituximab for adult patients with relapsed or refractory DLBCL after at least 2 previous therapies. Polatuzumab vedotin is an anti-CD79b antibody-drug conjugate linked to MMAE [monomethyl auristatin E], the same drug that’s in brentuximab vedotin,” John M. Burke, MD, explained.

Approval of polatuzumab vedotin was based on data from an open-label multicenter clinical trial (NCT02257567) that included 80 patients with relapsed or refractory DLBCL after at least 1 prior regimen.

Patients were randomly assigned 1:1 to receive polatuzumab vedotin with bendamustine/rituximab or bendamustine/rituximab for 6 cycles lasting 21 days each. At the end of therapy, the CR rate was 40% in the polatuzumab vedotin combination arm vs 18% in the bendamustine/rituximab arm. The best overall response rate (CRs and PRs) was 63% with the polatuzumab vedotin combination vs 25% with bendamustine/rituximab. Among the 25 patients who achieved PRs or CRs to the polatuzumab vedotin combination, responses lasted at least 6 months in 16 patients (64%) and at least 12 months in 12 patients (48%).

**TABLE 1.** TEAEs Per Patient Year of Exposure to L-MIND Treatment Regimen

<table>
<thead>
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<tr>
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<td>0.11</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>TEAE, treatment-emergent adverse effect</strong></td>
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</tbody>
</table>
impressed overall with this agent’s efficacy and sees it as an important therapy for patients with DLBCL.

**SELINEXOR**

On June 22, 2020, the FDA granted accelerated approval to selinexor for adult patients with relapsed or refractory DLBCL, including DLBCL arising from follicular lymphoma, with relapsed or refractory DLBCL, including approved to selinexor for adult patients with relapsed or refractory chronic lymphocytic leukemia or aggressive forms of non-Hodgkin lymphoma.

Selinexor is a selective inhibitor of nuclear export. In addition to its unique mechanism action, it is novel because it is taken orally. Flinn and Maddocks both noted that its oral formulation makes it an attractive treatment option.

Approval of selinexor was based on SADAL (NCT02272751), a multicenter, single-arm, open-label, phase 2 trial that included 127 patients with DLBCL who had previously received 2 to 5 systemic regimens. Patients took 60 mg of selinexor orally on days 1 and 3 weekly until disease progression or unacceptable toxicity. The overall response rate was 28% (n = 36). There were 15 (12%) CRs and 21 (17%) PRs.

“The responses are probably less impressive than what we’ve seen with some of the other drugs that we’re mentioning that have become available in the last couple of years for relapsed disease. Moving forward, selinexor may potentially be combinable with chemotherapy or other drugs. That may really be the future of this drug—to combine it with some of the other therapies that are out there to see if they can improve efficacy,” Burke said. Multiple such studies are ongoing (**TABLE 2**).

The most common grade 3 to 4 TEAEs with selinexor included thrombocytopenia, neutropenia, anemia, fatigue, hyponatremia, and nausea. The most common serious AE included pyrexia, pneumonia, and sepsis. No deaths were attributed to treatment with selinexor. Based on its safety profile, Maddocks said, “[this treatment] does require some work,” with use of various premedications needed. However, with the use of such agents, she noted that the regimen appears tolerable.

Patient selection for this treatment presents a clinical challenge, especially with other more-efficacious options available. “To me, this is something that you can consider if you have a patient who relapses after CAR T-cell therapy, isn’t eligible for a trial, wants to try something, or maybe if you have an older patient who is not eligible for transplant, is not eligible for CAR T, and wants to try something,” Maddocks said, noting that she has not used it for any of her patients. “I would say that in the second-line setting, for somebody who’s not going to be eligible for a curative therapy, I’m using tafasitamab-lenalidomide or, prior to that, if I could get access to it, BR [bendamustine-rituximab]-polatuzumab vedotin,” she said.

**TABLE 2.** Clinical Trials Recruiting Patients to Assess Selinexor Combinations for Relapsed/Refractory DLBCL

<table>
<thead>
<tr>
<th>ClinicalTrials.gov identifier</th>
<th>Regimen</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04607772</td>
<td>Selinexor + backbone treatments or novel therapies</td>
<td>1/2</td>
</tr>
<tr>
<td>Arm A: Selinexor + bendamustine/rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Selinexor + polatuzumab vedotin/rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm C: Selinexor + polatuzumab vedotin/bendamustine/rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm D: Selinexor + rituximab/gemcitabine/oxaliplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm E: Selinexor + ibritinib/rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm F: Selinexor + lenalidomide/rituximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm G: Selinexor + lenalidomide/tafasitamab</td>
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<td></td>
</tr>
<tr>
<td>Arm H: Selinexor + venetoclax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04442022</td>
<td>Rituximab-gemcitabine-dexamethasone-platinum ± selinexor</td>
<td>2/3</td>
</tr>
<tr>
<td>NCT03955783*</td>
<td>Venetoclax + selinexor</td>
<td>1</td>
</tr>
<tr>
<td>NCT03147885*</td>
<td>Selinexor + R-CHOP</td>
<td>1/2</td>
</tr>
<tr>
<td>NCT02303392*</td>
<td>Selinexor + ibritinib</td>
<td>1</td>
</tr>
</tbody>
</table>

DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

*Includes patients with other high-risk hematologic malignancies.

†Includes patients with a variety of advanced B-cell non-Hodgkin lymphomas.

‡Includes patients with relapsed/refractory chronic lymphocytic leukemia or aggressive forms of non-Hodgkin lymphoma.

Mehta noted that several case reports of central nervous system penetration have been reported with selinexor. He said that he also has seen responses in patients with central nervous system involvement, making this a possible additional niche for this drug, although data from ongoing studies are needed to provide more definitive information.

**REFERENCES**


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