COVID-19 Sharpens Focus on Drug Holidays
BLENREP
belantamab mafodotin-blmf
for injection 100 mg

NOW APPROVED

Please see following pages for Brief Summary of full Prescribing Information, including BOXED WARNING

Trademarks are owned by or licensed to the GSK group of companies.

©2020 GSK or licensor.
BLMJRNA200002 August 2020
Produced in USA.

Learn more today at BLENREPHCP.com
**INDICATIONS AND USAGE**

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate improvements in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate improvements in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

Perform an ophthalmic exam prior to initiation of BLENREP and during treatment [see Warnings and Precautions (5.1)].

Advise patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist [see Warnings and Precautions (5.1)].

2.2 Recommended Dosage

The recommended dosage of BLENREP is 2.5 mg/kg of actual body weight given as an intravenous infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.

2.3 Dosage Modifications for Adverse Reactions

The recommended dose reduction for adverse reactions is:

- BLENREP 1.9 mg/kg intravenously once every 3 weeks.

Discontinue BLENREP in patients who are unable to tolerate a dose of 1.9 mg/kg (see Tables 1 and 2).

**Corneal Adverse Reactions**

The recommended dosage modifications for corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA), are provided in Table 1 [see Warnings and Precautions (5.1)]. Determine the recommended dosage modification of BLENREP based on the worst finding in the worst affected eye. Worst finding should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity (KVA) scale.

**Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale**

<table>
<thead>
<tr>
<th>Corneal Adverse Reaction</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal examination finding(s): Mild superficial keratopathya</td>
<td>Continue treatment at current dose.</td>
</tr>
<tr>
<td>Change in BCVA: Decline from baseline of 1 line on Snellen Visual Acuity</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
</tr>
<tr>
<td>Corneal examination finding(s): Moderate superficial keratopathya</td>
<td>Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at same dose.</td>
</tr>
<tr>
<td>Change in BCVA: Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
</tbody>
</table>

*a Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

*b Changes in visual acuity due to treatment-related corneal findings.

*c Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

*d Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

*e Corneal epithelial defect such as corneal ulcers.

3. ADVERSE REACTIONS

The recommended dosage modifications for other adverse reactions are provided in Table 2.

**Table 2. Dosage Modifications for Other Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia [see Warnings and Precautions (5.3)]</td>
<td>Platelet count 25,000 to less than 50,000/mcL</td>
<td>Consider withholding BLENREP and/or reducing the dose of BLENREP.</td>
</tr>
<tr>
<td>Infusion-related reactions [see Warnings and Precautions (5.4)]</td>
<td>Grade 2 (moderate) or Grade 3 (severe)</td>
<td>Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%.</td>
</tr>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 4 (life-threatening)</td>
<td>Permanently discontinue BLENREP and provide emergency care.</td>
</tr>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 3</td>
<td>Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.</td>
</tr>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 4</td>
<td>Consider permanent discontinuation of BLENREP if continuing treatment, withhold BLENREP until improvement to Grade 1 or better and resume at reduced dose.</td>
</tr>
</tbody>
</table>

2.4 Preparation and Administration

BLENREP is a hazardous drug. Follow applicable special handling and disposal procedures.1

Calculate the dose (mg), total volume (mL) of solution required, and the number of vials of BLENREP needed based on the patient’s actual body weight. More than 1 vial may be needed for a full dose. Do not round down for partial vials.

**Reconstitution**

- Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (68ºF to 77ºF [20ºC to 25ºC]).
- Reconstitute each 100-mg vial of BLENREP with 2 mL of Sterile Water for Injection, USP to obtain a final concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. Do not shake.
- If the reconstituted solution is not used immediately, store refrigerated at 36ºF to 46ºF (2ºC to 8ºC) or at room temperature (68ºF to 77ºF [20ºC to 25ºC]) for up to 4 hours in the original container. Discard if not diluted within 4 hours. Do not freeze.

(continued on next page)
• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to opalescent, colorless to yellow to brown liquid. Discard if extraneous particulate matter is observed.

**Dilution**

• Withdraw the calculated volume of BLENREP from the appropriate number of vials and dilute in a 250-mL infusion bag of 0.9% Sodium Chloride Injection, USP, to a final concentration of 0.2 mg/mL to 2 mg/mL. The infusion bags must be made of polyvinylchloride (PVC) or polyolefin (PO).

• Mix the diluted solution by gentle inversion. Do not shake.

• Discard any unused reconstituted solution of BLENREP left in the vial(s).

• If the diluted infusion solution is not used immediately, store refrigerated at 36ºF to 46ºF (2ºC to 8ºC) for up to 24 hours. Do not freeze. Once removed from refrigeration, administer the diluted infusion solution of BLENREP within 6 hours (including infusion time).

• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted infusion solution should be clear and colorless. Discard if particulate matter is observed.

**Administration**

• If refrigerated, allow the diluted infusion solution to equilibrate to room temperature (68ºF to 77ºF [20ºC to 25ºC]) prior to administration. Diluted infusion solution may be kept at room temperature for no more than 6 hours (including infusion time).

• Administer by intravenous infusion over approximately 30 minutes using an infusion set made of polyvinyl chloride (PVC) or polyolefin (PO).

• Filtration of the diluted solution is not required; however, if the diluted solution is filtered, use a polysulfonetherephlene (PES)-based filter (0.2 micron).

Do not mix or administer BLENREP as an infusion with other products. The product does not contain a preservative.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

**Keratopathy**

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

**Visual Acuity Changes**

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

**Monitoring and Patient Instruction**

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3)]. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1)].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].

5.2 BLENREP REMS

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)]. Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENREPREMS.com and 1-855-209-9188.

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood count checks at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3)]

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)]. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3)]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

- Ocular toxicity [see Warnings and Precautions (5.1)].
- Thrombocytopenia [see Warnings and Precautions (5.3)].
- Infusion-related reactions [see Warnings and Precautions (5.4)].

6.1 Clinical Trials Experience

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

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.
Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2. [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (N = 95). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 2.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (>20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade ≥3 laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

### Table 3. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N = 95</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratopathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Decreased visual acuity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Blurred vision&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dry eyes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>21</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

<sup>b</sup> Visual acuity changes were determined upon eye examination.

<sup>c</sup> Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

<sup>d</sup> Dry eyes included dry eye, ocular discomfort, and eye pruritus.

<sup>e</sup> Fatigue included fatigue and asthenia.

Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (>20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade ≥3 laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

### Table 3. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>N = 95</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase increased</td>
<td>22</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2724 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-bli, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells. [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-bli may have the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women or in women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

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

**Data**

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-bli. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation
Risk Summary
There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential
BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

Pregnancy Testing
Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception
Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.
Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility
Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats [see Nonclinical Toxicology (13.1) of full Prescribing Information].

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

8.5 Geriatric Use
Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73m² as estimated by the Modification of Diet in Renal Disease (MDRD) equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST]) >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).
The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

15 REFERENCES
1. *OSHA Hazardous Drugs,* OSHA

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

Ocular Toxicity
- Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
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 48.
COVID-19 Sharpened Focus on Drug Holidays

by MEIR RINDE

Although drug holidays and treatment breaks are common features of cancer care in many malignancies, evidence about the efficacy of these strategies varies. A registry that the American Society of Clinical Oncology launched to analyze the impact of coronavirus disease 2019 (COVID-19) in oncology may offer fresh insights into the impact of therapy interruptions. Meanwhile, investigators are exploring biomarker-driven models for personalizing dosing.
ALTHOUGH ADVANCEMENTS IN PRECISION MEDICINE have transformed cancer care during the last 15 years, many questions remain about the optimal use of the remarkable therapies that have been added to clinical toolkits for a range of malignancies. These include identifying dosing strategies in the real-world care of individual patients, how best to sequence therapies, and when to stop or restart treatment.

The research paradigm now involves extensive molecular and pharmacogenomics testing in the development phase of new therapeutic strategies. However, patients are introduced to these treatments at standard doses, regardless of their individual characteristics, French investigators contended in a recent article.  

“Indeed, rather surprisingly, once the drug or combination of drugs has been carefully selected, in most cases the very concepts of precision medicine and personalized therapy seem all to have vanished into thin air, unfortunately,” Ferrer et al wrote.  

One aspect of this clinical conundrum is whether patients can safely take a break from therapy—a drug holiday—and still derive benefit from their treatment. Although intermittent breaks from therapy are common in some malignancies, evidence about the efficacy of such strategies varies and is sometimes inconclusive, according to experts interviewed for our cover story in this issue of OncologyLive.

In some ways, the disruptions in cancer care routines wreaked by the coronavirus disease 2019 pandemic might help shed light on the impact of therapy breaks. The American Society of Clinical Oncology has established a registry to collect data on how the pandemic is affecting the delivery of care and patient outcomes. However, long before this public health emergency, investigators had been delving into ways to improve approaches to administering therapy. Research teams at Cleveland Clinic Taussig Cancer Center in Ohio and Moffitt Cancer Center in Florida, for instance, are looking at models that track the evolution of a cancer in an individual patient. The result would be adaptive dosing strategies based on biomarkers that could help inform therapy decisions throughout multiple lines of treatment.

The importance of developing such approaches to care has become more important now that many cancers are chronic diseases. Our editorial team is committed to following these fascinating developments in our publications and on OncLive.com.

As always, thank you for reading.

Mike Hennessy Sr  
Chairman and Founder

REFERENCES


DISCOVER THE FIRST AND ONLY ERYTHROID MATURATION AGENT
FDA APPROVED FOR ANEMIA

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

for patients with ring sideroblasts who are failing an ESA and require ≥2 RBC units/8 weeks

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism
In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension
Hypertension was reported in 7% (6/81) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 6%. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity
REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

ADVERSE REACTIONS

Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients.

The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection.

LACTATION

It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

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


Learn more, sign up for updates, and find out how to access REBLOZYL at: REBLOZYLpro.com/discoverMDS

© 2020 Celgene Corporation.
REBLOZYL is a trademark of Celgene Corporation, a Bristol Myers Squibb company.
REBLOZYL is licensed from Acceleron Pharma Inc.
10/20 US-RR2-20-0461
REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use

Initial U.S. Approval: 2019

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE

1.2 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

REBLOZYL® (luspatercept-aamt) is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring ≥2 or more red blood cell units over 8 weeks in adults with very low-to-intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

1.3 Limitations Of Use

REBLOZYL® is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage for Myelodysplastic Syndromes with Ring Sideroblasts (MDS-RS) or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T) Associated Anemia

The recommended starting dose of REBLOZYL® is 1 mg/kg once every 3 weeks by subcutaneous injection for patients with anemia of MDS-RS or MDS/MPN-RS-T. Prior to each REBLOZYL® dose, review the patient’s hemoglobin and transfusion record. Titrate the dose based on responses according to Table 3. Interrupt treatment for adverse reactions as described in Table 4. Discontinue REBLOZYL® if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any dose.

If a planned administration of REBLOZYL® is delayed or missed, administer REBLOZYL® as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

Dose Modifications for Response

Assess and review hemoglobin results prior to each administration of REBLOZYL®. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation. If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the dose to 1.33 mg/kg. If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose level, increase the REBLOZYL® dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL® as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.

Dose modifications for response are provided in Table 3.

Table 3: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dose Titration for Response

<table>
<thead>
<tr>
<th>REBLOZYL Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Dose</strong></td>
</tr>
<tr>
<td>1 mg/kg every 3 weeks</td>
</tr>
<tr>
<td><strong>Dose Increases for Insufficient Response at Initiation of Treatment</strong></td>
</tr>
<tr>
<td>Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose</td>
</tr>
<tr>
<td>Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg</td>
</tr>
<tr>
<td>No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg</td>
</tr>
</tbody>
</table>

Table 4: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dosing Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>REBLOZYL Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3 or 4 hypersensitivity reactions</strong></td>
</tr>
<tr>
<td>Discontinue treatment</td>
</tr>
<tr>
<td><strong>Other Grade 3 or 4 adverse reactions</strong></td>
</tr>
<tr>
<td>Interrupt treatment</td>
</tr>
<tr>
<td>When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level**</td>
</tr>
<tr>
<td>If the dose delay is &gt;12 consecutive weeks, discontinue treatment</td>
</tr>
</tbody>
</table>

**Table 4: Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 4.

3 ADVERSE REACTIONS

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

- Thrombosis/Thromboembolism
- Hypertension

Based on findings from animal reproductive studies, REBLOZYL® may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposure (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.75 mg/kg.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with REBLOZYL® and for at least 3 months after the final dose (see Use in Specific Populations (8.1, 8.3)).

4 CONTRAINDICATIONS

None.

(Continued)
Other clinically relevant adverse reactions reported in <5% of patients include bronchitis, urinary tract infection, and hypertension [see Warnings and Precautions (5.2)].

Shifts from Grades 0-1 to Grades 2-4 abnormalities for selected laboratory tests during the first 8 cycles in the MEDALIST trial are shown in Table 9.

### Table 9: Selected Grades 2-4 Treatment-Emergent Laboratory Abnormalities Through Cycle 8 in the MEDALIST Trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REBLOZY (N=153)</th>
<th>Placebo (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT elevated</td>
<td>151 (13 (8)</td>
<td>74 (5 (7))</td>
</tr>
<tr>
<td>AST elevated</td>
<td>152 (6 (4)</td>
<td>76 (0 (0))</td>
</tr>
<tr>
<td>Total bilirubin elevated</td>
<td>140 (17 (12)</td>
<td>66 (3 (5))</td>
</tr>
<tr>
<td>Creatinine clearance reduced</td>
<td>113 (30 (27))</td>
<td>62 (13 (21))</td>
</tr>
</tbody>
</table>

- Number of patients at Grades 0-1 at baseline.
- ALT = alanine aminotransferase; AST = aspartate aminotransferase.

### 6.2 Immunogenicity

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

Of 284 patients with beta thalassemia who were treated with REBLOZY (luspatercept-aamt) and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.4%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 2 patients (0.7%) who had neutralizing antibodies.

Of 260 patients with MDS who were treated with REBLOZY and evaluable for the presence of anti-luspatercept-aamt antibodies, 23 patients (8.9%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 9 patients (3.5%) who had neutralizing antibodies.

Luspatercept-aamt serum concentration tended to decrease in the presence of neutralizing antibodies. There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept-aamt antibodies in REBLOZY, clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept-aamt antibodies.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on findings in animal reproduction studies, REBLOZY may cause fetal harm when administered to a pregnant woman. There are no available data on REBLOZY use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes including embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) (see Data). Advise pregnant women of the potential risk to a fetus.

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

**Date**

Animal Data

In embryo-fetal development studies, luspatercept-aamt was administered subcutaneously at 5, 15, or 30 mg/kg on gestation days 3 and 10 (rats) or 5, 20, or 40 mg/kg on gestation days 4 and 11 (rabbits). Effects in both species included reductions in numbers of live fetuses and fetal body weights, and increases in resorptions, post-implantation losses, and skeletal variations (such as asymmetric sternal centra in rats and angulated hyoid in rabbits). Effects were observed at exposures (based on AUC) approximately 7-times (rats) and 16-times (rabbits) the MRHD of 1.75 mg/kg.

In a pre- and postnatal development study, pregnant rats were administered luspatercept-aamt subcutaneously at 3, 10, or 30 mg/kg once every 2 weeks during organogenesis and through weaning, gestation day 6 through postnatal day 20. At all dose levels lower F1 pup body weights and adverse kidney findings (such as membranoproliferative glomerulonephritis, tubular atrophy/hypoplasia, and vessel ectasia occasionally associated with hemorraghe) were observed. These effects were observed at exposures (based on AUC) approximately 1.6-times the MRHD of 1.75 mg/kg.

**Lactation**

Risk Summary

Luspatercept-aamt was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are no data on the presence of REBLOZY 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 patients that breastfeeding is not recommended during treatment with REBLOZY, and for 3 months after the last dose.

**8.3 Females and Males of Reproductive Potential**

**Contraception**

Females

REBLOZY may cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of the potential risk to effect contraception during treatment with REBLOZY and for at least 3 months after the last dose.

**Infertility**

Females

Based on findings in animals, REBLOZY may impair female fertility [see Nonclinical Toxicology (13.1)]. Adverse effects on fertility in female rats were reversible after a 14-week recovery period.

**8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established. Based on findings in juvenile animals, REBLOZY is not recommended for use in pediatric patients [see Non-Clinical Toxicology (13.1)].

**8.5 Geriatric Use**

Clinical studies of REBLOZY in beta thalassemia did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

Clinical studies of REBLOZY for treatment of anemia in MDS-RS and MDS/MPN-RS-T included 206 (79%) patients ≥65 years of age and 93 (36%) patients ≥75 years of age. No differences in safety or effectiveness were observed between older (<65 years) and younger patients.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with luspatercept-aamt.

In a repeat-dose toxicity study, juvenile rats were administered luspatercept-aamt subcutaneously at 1, 3, or 10 mg/kg once every 2 weeks from postnatal day 7 to 91. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at 10 mg/kg resulting in exposures (based on area under the curve [AUC]) approximately 4.4 times the maximum recommended human dose (MRHD) of 1.75 mg/kg.

In a combined male and female fertility and early embryonic development study in rats, luspatercept-aamt was administered subcutaneously to animals at doses of 1 to 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-aamt-treated females. Effects on female fertility were observed at the highest dose with exposures (based on AUC) approximately 7-times the MRHD of 1.75 mg/kg. Adverse effects on fertility in female rats were reversible after a 14-week recovery period. No adverse effects were noted in male rats.

### 17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with REBLOZY.

#### Thromboembolic Events

Advise beta thalassemia patients of the potential risk of thromboembolic events. Review known risk factors for developing thromboembolic events and advise patients to reduce modifiable risk factors (e.g., smoking, use of oral contraceptives) [see Warnings and Precautions (5.1)].

#### Effects on Blood Pressure

Caution patients that REBLOZY may cause an increase in blood pressure [see Warnings and Precautions (5.2)].

#### Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving REBLOZY and for at least 3 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with REBLOZY [see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)].

#### Lactation

Advise females not to breastfeed during treatment with REBLOZY and for 3 months after the final dose [see Use in Specific Populations (8.2)].

---

**Table 8: Adverse Reactions (≥5%) in Patients Receiving REBLOZY with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8 (Continued)**

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>REBLOZY (N=153)</th>
<th>Placebo (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades n (%)</td>
<td>Grade 3 n (%)</td>
<td>All Grades n (%)</td>
</tr>
<tr>
<td>Injury and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>10 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>10 (7)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Influenza/influenza like illness</td>
<td>9 (6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Includes asthenic conditions.

*Reaction includes similar/grouped terms.
Pandemic Heightens Stress of Cancer Diagnosis

by MAURIE MARKMAN, MD

THE ERA OF CORONAVIRUS DISEASE

2019 has transformed health care in the United States and worldwide, including in the oncology arena. Concerns about the risks associated with spending time in a medical facility for a consultation, test, or procedure have had a substantially negative impact on visits for these services, including well-established cancer screening strategies. The repercussions of delays in diagnosing cancer, either through screening or the presence of early symptoms, and of required modifications in standard-of-care management paradigms are only now beginning to be fully appreciated.

It is not difficult, however, to understand the anxiety that a patient with cancer experiences upon being informed that their treatment will have to be delayed or changed because of the pandemic, as their trusted oncologist struggles to explain the rationale for new therapeutic recommendations and at the same time provide reassurance that the ultimate outcome will not be seriously jeopardized.

This stress will be added to the potentially serious psychological effects associated with a patient being informed that the diagnosis is cancer. Although overall outcomes for cancer treatment have unquestionably improved rather dramatically over the past several decades, the unnerving and frightening words of Susan Sontag in her landmark work “Illness as Metaphor” remain for many patients (and in a number of clinical settings) as relevant today as when they were written more than 40 years ago: “Someone who has had a coronary is at least as likely to die of another one within a few years as someone with cancer is likely to die soon from cancer. But no one thinks of concealing the truth from a cardiac patient: there is nothing shameful about a heart attack. Cancer patients are lied to, not just because the disease is (or is thought to be) a death sentence but because it is felt to be obscene— in the original meaning of that word: ill-omened, abominable, disgusting, offensive to the senses.”

Much has been written over the past several decades about various approaches that patients, with the assistance of their families, can employ to cope successfully with their cancer journey. One approach that I’ve observed during my 40 years as an oncologist is for the individual to be realistic but remain truly optimistic about the future, regardless of published survival statistics or the often inaccurate focus by many, including the media, on the median in survival curves as the anticipated outcome for an individual patient.

We see reports in high-impact journals where patients with objectively incurable cancers are described as frequently saying that “cure” is their goal, with commentary suggesting that these individuals have either received completely inaccurate data from their oncologists or that they border on the delusional in their beliefs despite being provided with accurate information. We even see reports where self-declared experts claim that many patients who are offered entry into early-phase cancer clinical trials suffer from a form of psychological derangement (or, again, have been given inaccurate information) because they quite mistakenly believe they will benefit substantially from study participation; the phenomenon is called therapeutic misconception.

Much can be said to refute the contention that the current generation of molecularly based early-stage cancer clinical trials lack therapeutic potential, but it is important to note that investigators are likely to miss a fundamental message in patients’ responses to surveys about participation in such studies. Although there will certainly be patients with advanced cancers who fail (or refuse) to understand the facts related to their disease, it is also very possible these individuals fully appreciate their status but still maintain a fervent hope for a favorable outcome, electing to be optimistic rather than pessimistic about their future.

And what is wrong with this? In fact, existing literature has revealed survival benefits associated with an optimistic perspective following the diagnosis of cancer in certain clinical settings. Further, there is evidence that when there is alignment between the treatment goals of patients and their oncologists, substantially less psychological distress is likely to occur.

How patients with cancer perceive the potential clinical usefulness of their treatment may also influence specific therapeutic outcomes, as has been shown in studies examining both the placebo (“positive”) and nocebo (“negative”) effects associated with various medications.

In summary, it is critical that the oncology community continue to examine the psychological impact of a diagnosis of cancer and its treatment, and learn to optimize approaches that may favorably influence the individual’s cancer journey, including issues of quality of life, emotional well-being, and survival.
Combination Therapy Advances Treatment Landscape for TNBC

The FDA has granted an accelerated approval to pembrolizumab (Keytruda) for use in combination with chemotherapy in the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (combined positive score ≥10) as determined by an FDA-approved test.

The companion diagnostic, PD-L1 IHC 22C3 pharmDx, developed by Dako North America, Inc, was also approved.

The regulatory decision was based on data from the KEYNOTE-355 trial (NCT02819518), in which patients with previously untreated locally recurrent inoperable or metastatic TNBC received pembrolizumab in combination with investigator’s choice of either nab-paclitaxel (Abraxane), paclitaxel, or gemcitabine/carboplatin compared with placebo plus 1 of the 3 chemotherapy agents.

At a median follow-up of 26.1 months, data showed that pembrolizumab plus chemotherapy resulted in a median progression-free survival of 9.7 months (95% CI, 7.6-11.3) versus 5.6 months (95% CI, 5.3-7.5) with placebo and chemotherapy (HR, 0.65; 95% CI, 0.49-0.86; one-sided P = .0012).

Additionally, in patients whose tumors had a PD-L1 combined positive score of 1 or higher, the median progression-free survival was 7.6 months with pembrolizumab and chemotherapy versus 5.6 months with chemotherapy alone (HR, 0.74; 95% CI, 0.61-0.90; P = .0014), although this was not determined to be statistically significant.

TO READ MORE, VISIT https://bit.ly/3AoGUF.

FoundationOne Liquid CDx Companion Diagnostic Tags on Olaparib for mCRPC

The FDA has granted approval for FoundationOne Liquid CDx to be used as a companion diagnostic for olaparib (Lynparza) for select patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene–mutated metastatic castration-resistant prostate cancer (mCRPC). The diagnostic will use a blood-based biopsy to identify patients with mCRPC who harbor BRCA1, BRCA2, and/or ATM alterations and may be appropriate candidates for treatment with the PARP inhibitor.

Olaparib received regulatory approval in May 2020 for patients with deleterious or suspected deleterious germline or somatic HRR gene–mutated mCRPC who have progressed on previous treatment with either enzalutamide (Xtandi) or abiraterone acetate (Zytiga), based on data from the phase 3 PROfound trial (NCT02987543).

Results showed that the agent reduced the risk of disease progression or death by 66% compared with abiraterone acetate or enzalutamide (HR, 0.34; 95% CI, 0.25-0.47; P < .0001) in patients with BRCA1/2- or ATM-mutated mCRPC.

FoundationOne Liquid CDx added 3 targeted therapies in several tumor types to its indications in October 2020, including alpelisib (Piqray) in advanced or metastatic breast cancer, rucaparib (Rubraca) in advanced ovarian cancer, and alectinib ( Alecensa) in ALK-mutated metastatic non–small-cell lung cancer.

In August 2020, the diagnostic was approved for Medicare/Medicaid coverage as a genomic profiling test across all solid tumors. The decision was based on analytical and clinical validation trials that collected more than 7500 samples and 30,000 unique variants across more than 30 tumor types. The test demonstrated high sensitivity and specificity, even at the low allele frequencies observed in the collected blood samples from various tumors.

TO READ MORE, VISIT https://bit.ly/2iptBTi.

USPSTF Lowers Screening Age, Recommends Test Options in Draft Guidance for CRC

New draft guidelines for patients with colorectal cancer (CRC) from the US Preventive Services Task Force (USPSTF) now recommend that screening begin 5 years earlier, at age 45 versus 50.

The grade B recommendation, which endorses screening for CRC in adults aged 45 to 49 years, also lists the noninvasive CRC screening test Cologuard as a recommended method for all average-risk adults between the ages of 45 and 75 years. CRC screening for adults aged 50 to 75 years remains a grade A recommendation.

“Unfortunately, not enough people in the US receive this effective preventive service that has been proven to save lives,” Alex Krist, MD, MPH, task force chair, said in a press release announcing the draft guidance. “We hope that this recommendation to screen people ages 45 to 75 for colorectal cancer will encourage more screening and reduce people’s risk of dying from this disease.”

“Exact Sciences commends the members of the USPSTF for lowering the screening age and recommending Cologuard among multiple screening test options,” said Kevin Conroy, chairman and CEO of Exact Sciences. “The confidence and influence of the guidelines will without a doubt encourage more clinicians to offer screening to their patients starting at 45.”

Cologuard uses a biomarker panel to assess an individual stool sample for 10 DNA markers, such as aberrantly methylated BMP3 and NDRG4 promoter regions, KRAS mutations, β-actin, and hemoglobin. In August 2014, Cologuard became the first FDA-approved stool DNA screening test for CRC, receiving inclusion in the USPSTF screening guidelines for those over the age of 50 years.

In September 2019, the FDA expanded Cologuard’s approval to include eligible at-risk adults 45 years or older. The expanded indication of the at-home stool-based screening assay applies to approximately 19 million average-risk individuals in the United States between ages 45 and 49 years.

Research presented at the 2020 American College of Gastroenterology (ACG) Annual Scientific Meeting indicated that cancer screening rates have risen since 2014, largely attributable to the approval and use of Cologuard.

In the retrospective analysis, investigators evaluated CRC screening based on IBM MarketScan claims that had been made between August 2011 and July 2019. The study included 60,770 average-risk patients aged 50 to 75 years who were enrolled in their health plan in the past decade.

Between 50% and 70% of these patients were up-to-date with screening, with increasing proportions each year. Among patients newly screened, multitarget stool DNA (Cologuard) uptake increased from 2% in 2016 to 15% in 2018.

The public comment period for the draft guidance closed on November 23, 2020. The task force has not identified a date for a final decision on the recommendations.

TO READ MORE, VISIT https://bit.ly/3kmPNd.
THE APPROVAL OF LUSPATERCEPT-AAMT (Reblozyl) for the treatment of anemia in patients with myelodysplastic syndromes (MDS) offers a new option to reduce red blood cell (RBC) transfusion dependence, which, in addition to affecting the majority of these patients, can lead to serious health complications such as transfusion site reactions and infections.¹

On April 3, 2020, the FDA approved luspatercept for the treatment of anemia failing an erythropoiesis-stimulating agent (ESA) and requiring 2 or more RBC units over 8 weeks in adults with very low- to intermediate-risk MDS with ring sideroblasts (MDS-RS) or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).²

The approval for the erythroid maturation agent was based on efficacy results from the phase 3 MEDALIST trial (NCT02631070), which showed that treatment with luspatercept increased RBC-transfusion independence (RBC-TI) among patients with MDS-RS.

In an interview with OncologyLive®, Joseph G. Jurcic, MD, director of the Hematologic Malignancies Section of the Division of Hematology/Oncology, and professor of medicine at Columbia University Medical Center in New York, New York, discussed strategies to optimize patient selection for luspatercept.

Q Please expand upon the characteristics of this patient population and the efficacy data that led to the approval.

In [MDS/MPN], RS must comprise 15% of the total nucleated cells in the marrow, or 5% of the total nucleated cells in the presence of an SF3B1 mutation. Older studies reported RS in only 10% of MDS patients, but the numbers may be higher. For example, a more recent study showed SF3B1 mutations in up to 30% of patients with MDS and 20% of patients with MDS/MPN.³ It is important to accurately diagnose MDS with RS. If you look for RS, you will diagnose it at a greater frequency.

Interestingly, the MPN-RS-T population [for which luspatercept is approved] was not included in the MEDALIST study but has a lot of biologic similarities with the study population.

In the [MEDALIST] trial, patients with very low-risk, low-risk, or intermediate-risk MDS-RS defined according to the Revised International Prognostic Scoring System who had been receiving regular RBC transfusions were randomized to receive either luspatercept at a dose of 1.0 mg/kg up to 1.75 mg/kg or placebo, administered subcutaneously every 3 weeks.

Investigators randomly assigned 153 patients to receive luspatercept and 76 to receive placebo. TI greater than 8 weeks was observed in 38% of the patients in the luspatercept group, compared with 13% of those in the placebo group. A higher percentage of patients in the luspatercept group than in the placebo group were TI for weeks 1 to 24 [28% vs 8%] and weeks 1 to 48 [33% vs 12%].

Q How does luspatercept enact its anticancer activity?

Luspatercept is a recombinant fusion protein derived from human activin receptor type IIb and linked to a protein derived from immunoglobulin G. Luspatercept has a completely different mechanism of action than ESAs. The agent binds transforming growth factor β superfamily ligands [to] reduce SMAD2 and SMAD3 signaling, which contributes to ineffective erythropoiesis.

Q What adverse effects do health care providers need to be aware of?

In general, the drug is well tolerated. The most common luspatercept-associated adverse effects [AEs] are fatigue, diarrhea, asthenia, nausea, and dizziness. The incidence of these effects decreased over time. This was particularly true in individuals who experienced fatigue, which can be seen in up to 20% of patients. Clinicians need to be aware of fatigue. They need to warn the patients ahead of time to stick with luspatercept: the fatigue is going to [attenuate] and patients will hopefully have responded after the first 1 or 2 injections. Their anemia will improve, and so will their overall fatigue with a little more time. Fatigue resolves quickly, in just a few weeks.

Q Are there any factors to consider as to how this agent will fit into the current treatment paradigm?

Lower risk patients with MDS with del(5q) [deletion 5q] should still receive lenalidomide [Revlimid], but the majority do not have del(5q). Lower-risk patients without del(5q), anemia, and an erythropoietin level less than 500 should receive a 3-month trial of an ESA with or without a granulocyte-colony-stimulating factor.

Prior to luspatercept’s approval, therapeutic options were limited either to single-agent lenalidomide or lenalidomide with ESAs. Hypomethylating agents have also been used but come with AEs. Open questions currently include the utility of luspatercept in lower risk MDS patients without RS and whether luspatercept would be more effective than ESAs as first-line therapy.

Q How can the benefit of luspatercept be optimized in this patient population?

It is important for clinicians to work closely with pathologists to accurately diagnose MDS-RS. The number of RS must be quantified in reports. It can be a bit tricky to determine who has MDS with rings that are sideroblasts, and this is not always well highlighted in pathology reports. It is critically important that the number of rings that are sideroblasts are quantified. In order to accurately diagnose this disease, you need to see 15% RS in the marrow. Clinicians really need to push the pathologists to give them that information so they can accurately diagnose this disorder.

[Further, the] availability of luspatercept also points out the need for routine molecular testing to identify patients with SF3B1 who may benefit from luspatercept. Molecular testing is crucial in determining what treatments patients will respond to. Clinicians need to conduct molecular tests to identify the patients who might respond to luspatercept. All patients with MDS should undergo molecular typing at the time of diagnosis.

REFERENCES
FDA grants approval for the erythroid maturation agent luspatercept-aamt (Reblozyl) for the treatment of anemia failing an erythropoiesis-stimulating agent (ESA) and requiring 2 or more red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with MDS/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

Mechanism of action:
- Luspatercept is a recombinant fusion protein that binds several endogenous transforming growth factor-β superfamily ligands to diminish signaling from the SMAD2-SMAD3 pathway.

How supplied:
- A white to off-white lyophilized powder contained in a single-dose 25- or 75-mg vial

Company: Celgene Corporation

PIVOTAL CLINICAL TRIAL
MEDALIST (NCT02631070), a phase 3 multicenter, placebo-controlled trial, enrolled 229 patients with MDS that meet Revised International Prognostic Scoring System criteria for very–low-, low-, or intermediate-risk disease. Patients with these MDS classifications who also had RS, required RBC transfusions (≥ 2 RBC units over 8 weeks), and demonstrated an inadequate response to prior treatment with an ESA, were unable to tolerate ESAs, or had a serum erythropoietin greater than 200 units per liter were eligible to participate.

Efficacy Results in the MEDALIST Trial

<table>
<thead>
<tr>
<th>End point</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
<th>Common risk difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-TI ≥ 8 weeks during weeks 1-24</td>
<td>37.9%</td>
<td>13.2%</td>
<td>24.6 (14.5-34.6)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>RBC-TI ≥ 12 weeks during weeks 1-24</td>
<td>28.1%</td>
<td>7.9%</td>
<td>20.0 (10.9-29.1)</td>
<td>.0002</td>
</tr>
<tr>
<td>RBC-TI ≥ 12 weeks during weeks 1-48</td>
<td>33.3%</td>
<td>11.8%</td>
<td>21.4 (11.2-31.5)</td>
<td>.0003</td>
</tr>
</tbody>
</table>

RBC-TI, red blood cell-transfusion independent.

The median duration of treatment was 49 weeks (range, 6-114) in the luspatercept arm and 24 weeks (range, 7-89) in the placebo arm.

Commonly Reported Adverse Events in MEDALIST Study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
<th>All grades</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>41%</td>
<td>7%</td>
<td>22%</td>
<td>3%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>20%</td>
<td>2%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>18%</td>
<td>&lt; 1%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>&lt; 1%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16%</td>
<td>0%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>0%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13%</td>
<td>1%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>10%</td>
<td>&lt; 1%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>8%</td>
<td>2%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Syncope/presyncope</td>
<td>5%</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

- Blood pressure effects: Advise patients that luspatercept may increase blood pressure.
- Hypertension: Monitor blood pressure during treatment. Initiate antihypertensive treatment if necessary.
- Embryo-fetal toxicity and lactation: Luspatercept can cause fetal harm. Caution women of reproductive potential to use effective contraception and refrain from breastfeeding during treatment and for at least 3 months after the final dose.

**BASELINE PATIENT CHARACTERISTICS: Efficacy Population (N = 229)**

- Median age (years)
  - Luspatercept (n = 153): 71
  - Placebo (n = 76): 72

**Diagnosis per WHO criteria (%)**

- MDS-RS: Luspatercept 88.2%, Placebo 85.5%
- MDS/MPN-RS-T: Luspatercept 9.2%, Placebo 11.8%
- Other: Luspatercept 2.6%, Placebo 2.6%

REFERENCES

NCI Director Describes COVID-19 Response

by KRISTI ROSA

THE NATIONAL CANCER INSTITUTE (NCI) is helping battle the coronavirus disease 2019 (COVID-19) pandemic through several initiatives, according to Norman “Ned” E. Sharpless, MD, the agency’s director. These measures include investigating anticancer agents to treat patients with the disease, making clinical trials more flexible, and conducting critical serology research to increase understanding and inform future approaches.

More than 50 million COVID-19 cases and more than 1.2 million deaths from the disease have been reported worldwide, according to the World Health Organization. In the United States as of November 2020, the CDC has recorded more than 12 million cases, including over 250,000 deaths, since January 21, 2020.

Investigators are working to understand the impact of a COVID-19 diagnosis on patients with cancer. NCI-designated cancer centers are among more than 120 institutions that are part of the COVID-19 and Cancer Consortium (CCC19), which to collects and analyzes data on adult patients who have been diagnosed with COVID-19 and who have a history of cancer or who currently have an invasive solid tumor or hematologic malignancy.

The data have revealed factors associated with increased 30-day, all-cause mortality in patients with cancer and COVID-19: increased age, male sex, smoking status, treatment with hydroxychloroquine plus azithromycin versus treatment with neither, and 2 or more comorbidities requiring treatment. Factors that are not associated with increased mortality are race and ethnicity, obesity, type of malignancy, type and recency of anticancer treatment, and recent surgery (TABLE 4).

“The NCI has significant expertise…and a lot of external capabilities to do cutting-edge research in an emergency setting,” Sharpless said during a virtual presentation at the 38th Annual CFS. “As such, I think it was natural when the pandemic really got going that the NCI was asked to step in and help provide some scientific response.”

CARE DISRUPTIONS

A modeling effort performed earlier this year used the NCI’s Cancer Intervention and Surveillance Monitoring Network (CISNET) to better understand the impact of the pandemic on cancer screening, diagnosis, and therapy.

Investigators looked specifically at breast and colorectal cancers because their CISNET models were advanced, Sharpless said. Investigators projected that there would be an excess of 10,000 deaths from 2020 to 2030, or a 1% increase in mortality, over the next decade, Sharpless said. The same disruptions are believed to be at play in other malignancies, as well.

“We feel that the assumptions we made about the disruptions to care, were, if anything, conservative estimates, and the disruptions that we’re actually seeing in hospitals across the country are greater than what we had predicted back then in June,” Sharpless said. “This is something that we all have to bear in mind. We need to share some collective responsibility [to determine] how to preserve the cancer care enterprise during a pandemic and ensure that we’re not exchanging one public health crisis for another.”

During the pandemic, data have indicated that there has been a decline in cancer screenings, diagnoses, and decreased or deferred care. These disruptions likely will have long-term implications for cancer mortality, Sharpless stressed. To combat this, the oncology community needed to come together to find safe, innovative ways to prioritize care for patients, he added.

“We don’t want our patients to be at risk for COVID-19, nor their caregivers; however, we need to get back to business,” Sharpless said.

NCI TAKES ACTION

The NCI’s response to the pandemic includes repurposing anticancer drugs to treat COVID-19, launching the NCI COVID-19 in Cancer Patients Study (NCCAPS), providing special procedures for clinical trials, conducting serology research on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19,
TABLE. COVID-19 and Cancer: Patients With Active or Prior Malignancy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age: per 10 years</td>
<td>1.84 (1.53-2.21)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.63 (1.07-2.48)</td>
</tr>
<tr>
<td>Smoking status: former vs never smoker</td>
<td>1.60 (1.03-2.47)</td>
</tr>
<tr>
<td>Number of comorbidities: 2 vs 0</td>
<td>4.50 (1.33-15.28)</td>
</tr>
<tr>
<td>ECOG PS ≥2: 2 vs 0 or 1</td>
<td>3.89 (2.11-7.18)</td>
</tr>
<tr>
<td>Active cancer: progressing vs in remission</td>
<td>5.20 (2.77-9.77)</td>
</tr>
<tr>
<td>Azithromycin plus hydroxychloroquine: vs treatment with neither</td>
<td>2.93 (1.79-4.79)</td>
</tr>
</tbody>
</table>

*Within 30 days of COVID-19 diagnosis.
**Partially adjusted.
Confounding by indication cannot be excluded.

and offering flexibility and opportunities to study grantees.

Repurposing Cancer Drugs

Patients with severe COVID-19 infection frequently have a hyperinflammatory immune response that is indicative of macrophage activation. Since Bruton tyrosine kinase (BTK) is known to influence macrophage signaling and activation, investigators evaluated the selective BTK inhibitor acalabrutinib (Calquence) off-label in 19 hospitalized patients with severe COVID-19 infection; of these patients, 11 required supplemental oxygen, whereas 8 were on mechanical ventilation. After 10 to 14 days, the use of acalabrutinib was associated with an improvement in oxygenation in most of the patients.7

Despite these promising signals, acalabrutinib failed to improve outcomes for patients with COVID-19 in the phase 2 CALAVI trials (NCT04380688; NCT04346199), according to information released by AstraZeneca after Sharpless’ presentation.

Nevertheless, other anticancer therapies are under study in COVID-19 settings, including selinexor (Xpovio; NCT04349098) and the investigational agents leronlimab (NCT04347239) and pacritinib (NCT04404361).

Adapting Clinical Trial Efforts

Recognizing the challenges posed by the pandemic with regard to clinical trials, the NCI collaborated with the FDA to provide flexibility for their supported efforts. For example, patient care now can be transferred to different participating study sites. Local health care providers are able to provide study activities to encourage the continuity of care. Oral drugs now may be shipped from the NCI and trial sites directly to the study participant to decrease unnecessary risk. Remote informed consent via telephone has become acceptable in conjunction with a patient signature on a written document.

“We know that this has been a successful [effort]. Accrual on NCI therapeutic trials has largely returned to normal. We have polled investigators and they really like some of these flexibilities,” Sharpless said. “This is, perhaps, the silver lining of the pandemic. We’ve learned how to do trials in the modern era of Zoom chat and telehealth. We won’t forget those lessons. Many of these flexibilities will be good for clinical trials going forward and will affect how the NCI does business even after the pandemic is [over].”

Collecting Data

NCCAPS (NCT04387656) is a longitudinal natural history study of COVID-19 in patients with cancer. Investigators are collecting relevant data to better understand how the virus and its symptoms develop and evolve.4 The trial’s goal is to help inform the future treatment decisions for patients with cancer who also receive a diagnosis of COVID-19.

In the study, investigators gather blood samples to estimate antibody response and genetic susceptibility. These samples also will be used for biomarker development. The trial has a projected enrollment of 2000 patients.

“We launched this trial in about 6 weeks last spring, and it is now open at nearly 1000 sites in the United States. It has begun fairly robust accrual for patients with a history of cancer and COVID-19 infection,” Sharpless said. “We believe it will be very valuable to understand the biomarkers that predict bad outcomes in patients with cancer, as well as to understand the longitudinal history of this disease or the so-called long-haul COVID-19 conditions that we are now seeing in some patients.”

Joining Serology Research

In October 2020, the NCI launched the Serological Sciences Network (SeroNet) for COVID-19, with the goal of increasing the nation’s capacity for antibody testing and building a better understanding of immune response to the virus.9

“The NCI has a long history in serology research, and it has a fantastic [laboratory] that does serology research for human papillomavirus vaccine response; it was one of the standard study labs for the World Health Organization and other international agencies,” Sharpless said. “When the pandemic began, we repurposed that lab to become a SARS-CoV-2 coronavirus lab. [We wanted to] create a network to increase capacity for coronavirus testing and serology testing in the United States.”

The agency expects this SeroNet to engage more than 25 academic, government, and private sector biomedical research institutions. The US Congress authorized $306 million for the NCI to develop, validate, improve, and apply serological testing and associated technologies, according to the NCI.

Staying Flexible on Research Grants

The NCI has also channeled efforts to provide certain flexibilities for grantees who experienced disruptions to their research efforts.

“This has been [a] hard [time] for trainees who need to move to the next stage of their training or [who need to] get a job,” Sharpless noted. “This has also been difficult for scientists whose [laboratories] have been closed or whose clinical research efforts have been put on pause. The NCI, along with the broader National Institutes of Health [NIH], has been trying to send the message to grantees that we are going to allow every possible flexibility during the pandemic so that research can get back to normal as quickly as possible.”

These efforts include the NIH extending deadlines for applications, permitting institutions to use NCI grant funds to maintain salaries and stipends, extending project timelines, reporting requirements, and eligibility periods for early-stage investigators, and carrying over institutional training grants with previous approval.
1L ES-SCLC
TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

PD-L1+ mTNBC
TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1-stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

mTNBC=metastatic triple-negative breast cancer.

Important Safety Information
Serious Adverse Reactions
Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

- Immune-mediated pneumonitis. Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, have occurred. Permanently discontinue TECENTRIQ for Grade 3 or 4 pneumonitis
- Immune-mediated hepatitis. Immune-mediated hepatitis and liver test abnormalities, including fatal cases, have occurred. Permanently discontinue TECENTRIQ for AST or ALT elevations more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal
- Immune-mediated colitis. Immune-mediated diarrhea or colitis have occurred. Permanently discontinue TECENTRIQ for Grade 4 diarrhea or colitis
- Immune-mediated endocrinopathies. Thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, including diabetic ketoacidosis, and hypophysitis/hypopituitarism have occurred
- Other immune-mediated adverse reactions. TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. Permanently discontinue TECENTRIQ for Grade 4 immune-mediated adverse reactions involving a major organ
TECENTRIQ: THE COMMON THREAD IN IMPORTANT ADVANCEMENTS FOR LUNG AND BREAST CANCER TREATMENT

1L ES-SCLC

TECENTRIQ + carbo/etop
The first FDA-approved treatment for 1L ES-SCLC in 20 years¹,²

PD-L1+ mTNBC

TECENTRIQ + nab-pac
The first FDA-approved cancer immunotherapy combination in PD-L1+ mTNBC¹

*NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way. See the NCCN Guidelines® for detailed recommendations.

Category 1: based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Preferred intervention: interventions that are based on superior efficacy, safety, and evidence, and, when appropriate, affordability. Nab-paclitaxel (nab-pac) is also known as albumin-bound paclitaxel or paclitaxel protein-bound.

NCCN=National Comprehensive Cancer Network; PD-L1=programmed death-ligand 1.

+ Infections. Severe infections, including fatal cases, have occurred
+ Infusion-related reactions. Severe or life-threatening infusion-related reactions have occurred. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion-related reactions
+ Embryo-fetal toxicity. TECENTRIQ can cause fetal harm in pregnant women. Verify pregnancy status prior to initiating TECENTRIQ. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose
+ Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

Most Common Adverse Reactions
The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ in combination with other antineoplastic drugs for NSCLC and SCLC were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%), and decreased appetite (27%).

The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ with paclitaxel protein-bound for mTNBC were alopecia (56%), peripheral neuropathies (47%), fatigue (47%), nausea (46%), diarrhea (33%), anemia (28%), constipation (25%), cough (25%), headache (23%), neutropenia (21%), vomiting (20%), and decreased appetite (20%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.


Learn more at TECENTRIQ-HCP.com"
This indication is approved under accelerated approval based on tumor response rate and durability of response, and the indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Small Cell Lung Cancer

TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSqNSCLC) with PD-L1 TMB-Expressing tumors (TMB-E).

1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells (IC) covering > 1% of the tumor area), as determined by an FDA-approved test for PD-L1 expression.

TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSqNSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor alterations should have disease progression after EGFR or ALK inhibitor therapy.

1.4 Small Cell Lung Cancer

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

TECENTRIQ can cause pneumonitis and interstitial lung disease, defined as requiring use of systemic corticosteroids, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher pneumonitis, unless the pneumonitis is permanently discontinuous TECENTRIQ based on the severity (see Dosage and Administration (2.6)).

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent (see Adverse Reactions (6.1)), pneumonitis occurred in 2.5% of patients, including Grade 3 (0.8%), Grade 4 (0.1%), and Grade 5 (0.1%) immune-mediated pneumonitis. The median time to onset of pneumonitis was 16.6 months (range 1.0 day to 120 months). Pneumonitis resolved in 53% of patients, including 8.6% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (2 days to 14 days) followed by a taper. In clinical studies enrolling 2421 patients with NSqNSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy (see Adverse Reactions (6.3)), immune-mediated pneumonitis occurred in 5.5% of patients, including Grade 3 in 1.4% of patients. Pneumonitis was required in 4.2% of patients, including 3.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 5 days (1 day to 98 days) followed by a corticosteroid taper.

5.2 Immune-Mediated Hematologic

TECENTRIQ can cause fatal or severe infections and immune-mediated hematologic disorders. Monitor patients for signs and symptoms of infections, and in particular, after the last dose of TECENTRIQ as a single-agent (see Adverse Reactions (6.1)), infections occurred in 11% of patients, including Grades 3-4 in 0.3% of patients; 8.2% of the 2421 patients combination with platinum-based chemotherapy had hypophysitis occurred in < 0.1% of patients. The frequency and severity of hypophysitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSqNSCLC and SCLC.

5.3 Immune-Mediated Colitis

TECENTRIQ can cause severe or life-threatening pseudomembranous colitis. Monitor patients for early symptoms of pseudomembranous colitis. For Grade 2 or higher pseudomembranous colitis, interrupt or permanently discontinue TECENTRIQ (see Adverse Reactions (6.1)).

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent (see Adverse Reactions (6.1)), diarrhea or colitis occurred in 20% of patients, including Grade 3 (1.4%) event; median duration of diarrhea or colitis was 1.0 month (range 2 days to 110 months). Diarrhea or colitis resolved in 80% of the patients. Diarrhea or colitis led to discontinuation of TECENTRIQ in 0.2% of 2616 patients. Systemic corticosteroids were required in 1.1% of patients and high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 11 days) followed by a corticosteroid taper.

In clinical studies enrolling 2427 patients with NSqNSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy (see Adverse Reactions (6.3)), diarrhea or colitis occurred in 29% of patients. Systemic corticosteroids were required in 4.7% of patients, including 2.9% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 170 days) followed by a corticosteroid taper.

5.4 Immune-Mediated Endocrinopathies

TECENTRIQ can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, and hypophysitis/hypothalamic hypothyroidism.

In clinical studies enrolling 2427 patients with NSqNSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy (see Adverse Reactions (6.1)), hypothyroidism occurred in 11% of patients, including Grades 3–4 in 0.3% of patients; 8.2% of the 2421 patients combination with platinum-based chemotherapy had the use of hormone replacement therapy. Hypothyroidism occurred in 1.6% of patients. One patient experienced acute thyrotoxicosis.

In clinical studies enrolling 2421 patients with NSqNSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy (see Adverse Reactions (6.1)), hypothyroidism occurred in 11% of patients, including Grades 3–4 in 0.3% of patients; 8.2% of the 2421 patients combination with platinum-based chemotherapy had the use of hormone replacement therapy. Hypothyroidism and thyrotoxicosis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSqNSCLC and SCLC.

5.5 Other Immune-Mediated Adverse Reactions

TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions may persist after TECENTRIQ is discontinued during treatment with TECENTRIQ, immune-mediated adverse reactions can also manifest after discontinuation of TECENTRIQ.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For suspected Grade 3 or 4 immune-mediated adverse reactions, administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by taper. Or permanently discontinue TECENTRIQ, based on the severity (see Dose and Administration (2.6)).

If ulcers occur in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed in patients with TECENTRIQ. Ulcers may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Hypophysitis. Hypophysitis was infrequent and occurred in < 0.1% of patients. The frequency and severity of hypophysitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSqNSCLC and SCLC.

Type 1 Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt TECENTRIQ based on the severity (see Dose and Administration (2.6)).

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, type 1 diabetes mellitus occurred in 1% of patient. The frequency and severity of diabetes mellitus were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSqNSCLC and SCLC.

5.6 Infections

TECENTRIQ can cause severe infections and fatal infections. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable (see Dose and Administration (2.6)).

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent (see Adverse Reactions (6.1)), infections occurred in 30.4% of patients, including Grade 3 in 3.9% and Grade 4 in 1.5% in patients with untreated sarcoidosis. The most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients. The frequency and severity of infections were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSqNSCLC and SCLC.

5.7 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Infusion-related reactions may involve any organ system. While infusion-related reactions may persist after TECENTRIQ is discontinued during treatment with TECENTRIQ, infusion-related adverse reactions can also manifest after discontinuation of TECENTRIQ.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent (see Adverse Reactions (6.1)), infusion-related reactions occurred in 1.3% of patients, including Grade 3 in 0.2%. The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSqNSCLC and SCLC.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related reaction of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential to avoid pregnancy during TECENTRIQ treatment. Use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.2)).

6 ADVERSE REACTIONS

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

- Immune-Mediated Pneumonitis (see Warnings and Precautions (5.1))
- Immune-Mediated Hematologic (see Warnings and Precautions (5.2))
- Immune-Mediated Colitis (see Warnings and Precautions (5.3))
- Immune-Mediated Endocrinopathies (see Warnings and Precautions (5.4))
- Immune-Mediated Adverse Reactions (see Warnings and Precautions (5.5))
- Infections (see Warnings and Precautions (5.6))
- Infusion-Related Reactions (see Warnings and Precautions (5.7))
Tables 2 and 3 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion-related reaction, cough, abdominal pain (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (44%), decreased appetite (24%), nausea (24%), cough (15%), and diarrhea (22%). In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in 2427 patients who received ≥ 1 dose of TECENTRIQ in active-controlled trials, including IMpower150 and IMpower133. Among the 2421 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 26% were exposed for longer than 12 months. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks). The most common Grades 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, proteinuria, intestinal obstruction, sepsis, and pneumonia. TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation included diarrhea/colic (1.7%), fatigue (0.8%), hypertransaminasemia (0.6%), and dyspnea (0.6%). Adverse reactions leading to interruption occurred in 3.0% of patients; the most common (≥ 1%) were interstitial obstruction, fatigue, diarrhea, urinary tract infection, infusion-related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, urinary tract infection, pain, nausea, abdominal pain, back/neck pain, rash, cough, or peripheral edema.

### Table 2: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue1</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral edema2</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea3</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>0.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain4</td>
<td>15</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite1</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>Rash5</td>
<td>17</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection5</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough6</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea6</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Includes fatigue, asthenia, lethargy, and malaise
2 Includes edema, peripheral oedema, serous edema, lymphenema, and edema
3 Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
4 Includes decreased appetite and early satiety
5 Includes cough, dermatis, dermatitis acruminiform, rash maculo-papular, rash erythematous, rash puritic, rash macular, and rash papular
6 Includes urinary tract infection, urinary tract infection bacterial, cystitis, and ureopneumonia

### Table 3: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>15</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>10</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>7</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4</td>
</tr>
<tr>
<td>Increased AST</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0.3</td>
</tr>
</tbody>
</table>

1 Includes fever, chill, hepatomegaly, and malaise
2 Includes fatigue, dermatis, dermatis acruminiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
3 Includes urinary tract infection, urinary tract infection bacterial, cystitis, and ureopneumonia
4 Includes cough and productive cough
5 Includes dyspnea and exertional dyspnea

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen or who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen (see Clinical Studies [74]). Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common Grades 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, proteinuria, intestinal obstruction, urinary obstruction, hemorrhia, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

Adverse reactions leading to interruption occurred in 27% of patients; the most common (> 1%) were fever, asthenia, fatigue, proteinuria, urinary tract infection, urinary obstruction, abdominal pain, venous thromboembolism, sepsis, and pneumonia. TECENTRIQ was discontinued for adverse reactions in 3.2% of patients. Sepsis led to discontinuation in 0.6% of patients.

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (≥ 2%) were urinary tract infection, hemorrhia, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, and sepsis.

### Table 5: Adverse Reactions in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough4</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea5</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Includes fever, chill, hepatomegaly, and malaise
2 Includes fatigue, dermatis, dermatis acruminiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
3 Includes urinary tract infection, urinary tract infection bacterial, cystitis, and ureopneumonia
4 Includes cough and productive cough
5 Includes dyspnea and exertional dyspnea
paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min every 3 weeks for a maximum of 4 months, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.2)]. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

The most common Grades 3–4 adverse reactions (>2%) in patients receiving TECENTRIQ were fatigue, asthenia, hypertension, febrile neutropenia, diarrhea, pneumonia, nausea, decreased appetite, dehydration, and pulmonary embolism.

Table 6: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Increased ALAT</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Non-small Cell Lung Cancer (NSCLC)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Metastatic Non-Squamous NSCLC

The safety of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naive patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.2)]. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

The most common Grades 3–4 adverse reactions (>2%) in patients receiving TECENTRIQ were fatigue, asthenia, hypertension, febrile neutropenia, diarrhea, pneumonia, nausea, decreased appetite, dehydration, and pulmonary embolism.

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were febrile neutropenia, bronchocytopenia, fatigue, asthma, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hypocalcemia, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria. Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin in IMpower150. Study IMpower150 was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TECENTRIQ, as compared to the control arm, for any specified adverse reaction or laboratory abnormality listed in Tables 6 and 7.

Table 7: Laboratory Abnormalities Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>83</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Increased Creatine</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>3</td>
</tr>
</tbody>
</table>
The safety of TECENTRIQ in combination with paclitaxel protein-bound was evaluated in IMpassion130, a multicenter, international, randomized, double-blind placebo-controlled trial in patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic disease [see Clinical Studies (14.8)]. Patients received 840 mg of TECENTRIQ (n=432) or placebo (n=438) intravenously followed by paclitaxel protein-bound (100 mg/m²) intravenously for each 28 day cycle. TECENTRIQ was administered on days 1 and 15 and paclitaxel protein-bound was administered on days 1, 8, and 15 until disease progression or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to TECENTRIQ was 5.5 months (range: 0-32 months) and paclitaxel protein-bound was 5.1 months (range: 0-31.5 months) in the TECENTRIQ plus paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0-25.1 months) and paclitaxel protein-bound was 5.0 months (range: 0-23.7 months) in the placebo plus paclitaxel protein-bound arm.

The most common Grades 3-4 adverse reactions occurring in >2% were neutropenia (8%), peripheral neuropathies (9%), neutrophil count decreased (4.6%), fatigue (4%), anemia (2.9%), hypokalemia (2.2%), pneumonia (2.7%), and aspartate aminotransferase increased (2.0%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse reaction leading to TECENTRIQ discontinuation was peripheral neuropathy (<1%). Fatal adverse reactions occurred in 37% of patients receiving TECENTRIQ. Serious adverse reactions in >2% were neutropenia (4.5%), thrombocytopenia (3.5%), febrile neutropenia (2.5%), and thrombocytopenia (2.5%). TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in ≥2% of patients was infusion-related reactions (2.5%). Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (>2%) were neutropenia, neutrophil count decreased, hypokalemia, and pyrexia. Serious adverse reactions occurred in 23% (10/452) of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspepsia (1%), and pyrexia (1%). Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm.

Table 10 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ and paclitaxel protein-bound. Table 11 summarizes selected laboratory abnormalities worsening from baseline that occurred in at least 20% of patients in the TECENTRIQ treated patients.

Table 10: Adverse Reactions Occurring in >10% of Patients with TNBC

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ in combination with paclitaxel protein-bound (n=432)</th>
<th>Placebo in combination with paclitaxel protein-bound (n=438)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>58</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>General Disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>1.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with baseline available and at least one on-treatment laboratory test.

Small Cell Lung Cancer (SCLC)

The safety of TECENTRIQ with carboplatin and etoposide was evaluated in IMPower133, a randomized, multicenter, double-blind placebo-controlled trial in which 198 patients with ES-SCLC received TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.6)]. Among 198 patients receiving TECENTRIQ, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer. The most common Grades 3-4 adverse reactions (>2%) were fatigue, asthenia (7%), anemia (6%), neutropenia (5%), thrombocytopenia (5%), pneumonia (3.6%), and impaired renal function (2.6%). TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in ≥2% of patients was infusion-related reaction (2.5%). Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (>2%) were neutropenia (4.5%), thrombocytopenia (3.5%), febrile neutropenia (2.5%), and pneumonia (2.5%). TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in ≥2% of patients was infusion-related reaction (2.5%).
Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

### Table 12: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Carboplatin and Etoposide</th>
<th>Placebo with Carboplatin and Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>N = 198</td>
<td>N = 196</td>
</tr>
<tr>
<td>All Grades1 (%)</td>
<td>Grades 3–4 (%)</td>
<td>All Grades1 (%)</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Skin and Subcutaneous</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

### Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Carboplatin and Etoposide</th>
<th>Placebo with Carboplatin and Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>N = 198</td>
<td>N = 196</td>
</tr>
<tr>
<td>All Grades1 (%)</td>
<td>Grades 3–4 (%)</td>
<td>All Grades1 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>94</td>
<td>17</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>73</td>
<td>45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Increased Alkaline Phosphate</td>
<td>38 1</td>
<td>35 2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Increased Bilirubin</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Increased Lactate</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Increased Phosphates</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>21</td>
<td>7</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Risk Summary

Based on its mechanism of action (see Clinical Pharmacology (12.1)), TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death (see Data). Advise females of reproductive potential 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% to 4% and 15% to 20%, respectively.

#### 8.2 Lactation

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

#### 8.3 Females and Males of Reproductive Potential

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ (see Use in Specific Populations (8.1)).

#### Contraception

Females

Based on its mechanism of action, TECENTRIQ 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 TECENTRIQ and for at least 5 months following the last dose.

#### Male Fertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment (see Nonclinical Toxicology (13.5)).

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

Of 2461 patients with urothelial carcinoma, lung cancer, and triple-negative breast cancer who were treated with TECENTRIQ in clinical studies, 45% were 65 years or over and 11% were 75 years or over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older, and younger patients.

#### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

#### Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath (see Warnings and Precautions (5.2)).
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding (see Warnings and Precautions (5.3)).
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis (see Warnings and Precautions (5.5)).
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adrenal reactions (see Warnings and Precautions (5.5)).

#### Infections

Advise patients to contact their healthcare provider immediately for signs or symptoms of infection (see Warnings and Precautions (5.6)).

#### Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions (5.6)). Use in Specific Populations (8.1, 8.2).

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ (see Use in Specific Populations (8.3)).

#### Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose (see Use in Specific Populations (8.2)).
Novel Combinations Carry CDK4/6 Inhibitors Into the Future in HR+/HER2- Breast Cancer

by CAROLINE SEYMOUR

PATIENTS WITH ADVANCED HORMONE receptor-positive, HER2-negative breast cancer still face acquired resistance, even with the most effective agents, namely CDK4/6 inhibitors, which have demonstrated an unprecedented overall survival (OS) benefit in the metastatic setting. Investigators are now exploring pathways implicated in resistance, said Komal Jhaveri, MD, explaining that FGFR inhibitors, PI3K inhibitors, and selective estrogen receptor downregulators (SERDs) are just a few of the therapeutic classes under study in combination with CDK4/6 inhibitors as a means of overcoming drug resistance.

“We’re really trying to understand how to appropriately treat our patients and [determine] the next line of therapy for a patient who progresses on a CDK4/6 inhibitor. [To that end], we’re trying to understand the genomic alterations and next-generation sequencing data from tissue and plasma to better address that question,” Jhaveri, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, said in an interview with OncologyLive®.

During a presentation at the 38th Annual CFS® virtual conference Jhaveri expanded on the actionable alterations in patients with hormone receptor-positive, HER2-negative breast cancer (TABLE). She also discussed novel combinations that are under investigation, and spoke to the profound effects that CDK4/6 inhibitors have had on the field.

“The unprecedented, near doubling if not more of progression-free survival compared with endocrine therapy alone in the first-line setting has certainly changed our treatment paradigm,” said Jhaveri. “For patients who haven’t seen a CDK4/6 inhibitor in the first line, even in the second-line setting, we’ve been able to show a statistically significant progression-free [survival] benefit, justifying the use of this class of agents in the first- or second-line settings.”

At the European Society for Medical Oncology Congress 2019, 2 approved CDK4/6 inhibitors—ribociclib (Kisqali) and abemaciclib (Verzenio)—were shown to prolong OS as well. According to findings from the phase 3 MONALEESA-3 trial (NCT02422615), the median OS was not reached with ribociclib versus 40 months with endocrine therapy alone as first-line therapy in premenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer (HR, 0.71; 95% CI, 0.54-0.95; P = .00973). Moreover, in the phase 3 MONARCH 2 trial (NCT02107703), abemaciclib led to a median OS of 46.7 months versus 37.3 months with fulvestrant alone in patients with advanced hormone receptor–positive, HER2-negative breast cancer who progressed on prior endocrine therapy (HR, 0.757; 95% CI, 0.606-0.945; P = .01).

Such findings have set the stage for investigation into combinations with CDK4/6 inhibitors and novel targets, such as FGFR, Jhaveri explained.

“There is some [indication] from the...
have had at least 1 line of therapy in the metastatic setting. Notably, prior CDK4/6 inhibition will not serve as an exclusion criterion. As such, the preliminary results from the trial, which will be presented at the 2020 San Antonio Breast Cancer Symposium, will not only illustrate the activity of the triplet in an FGFR-amplified population but also potentially inform the utility of continuing CDK4/6 inhibition upon progression.

“There are many important questions that we’re still now trying to understand in the clinic, and these research efforts are underway, including whether there’s a role for continuing CDK4/6 beyond progression,” said Jhaveri. “The paradigm that we use in HER2-positive metastatic breast cancer is that targeting the HER2 pathway remains important and we continue anti-HER2 therapy beyond progression. The same is not yet clear for the utilization of CDK4/6 inhibitors beyond CDK4/6 [progression]. That’s something we’re actively evaluating in ongoing trials, such as MAINTAIN [NCT02632045].”

Another approach under investigation is that of combined PI3K and CDK4/6 inhibition, explained Jhaveri. “CDK4/6 is downstream of the PI3K/AKT/mTOR pathway, so if one were to consider dually vertically inhibiting these pathways together, we might be able to see better synergistic activity,” she said.

Key trials in this regard include PASTOR (NCT02599714), PIPA (NCT02389842), LeeBLet (NCT02154776), and TRINITI-1 (NCT02732119), among others.

ESR1 mutations are another viable target, arising in approximately 30% of women who have received prior aromatase inhibitors. “Our group and others have shown that these [mutations] are activating rare and primary tumors and seen mostly in the acquired setting after progression on aromatase inhibitor therapy,” Jhaveri said, adding that the prevalence observed in cell-free DNA ranges upward to approximately 40%. Oral SERDs are currently the subject of investigation in this setting, but whether they will pan out, either as single agents or in combination, has yet to be determined, said Jhaveri.

Although the data are still in early stages, findings from a phase 1/1b trial (NCT02734615) indicated that the oral SERD LSZ102 was well tolerated and was active in combination with ribociclib or alpelisib (Piqray) in patients with ER-positive breast cancer who had progressed on endocrine therapy. In the 3-arm study, investigators evaluated LSZ102 alone (arm A), in combination with ribociclib (arm B), and in combination with alpelisib (arm C). In arm A, LSZ102 elicited an objective response rate (ORR) of 1.3%, a clinical benefit rate (CBR) of 9.1%, and a median progression-free survival (PFS) of 1.8 months (95% CI, 1.7-2.0).5

In arm B, the addition of LSZ102 to ribociclib led to a 15.8% ORR and a CBR of 35.5%; the median PFS was 6.2 months (95% CI, 4.4-6.4). The combination of LSZ102 and alpelisib demonstrated an ORR of 5.4%, a CBR of 18.9%, and a median PFS of 3.5 months (95% CI, 1.8-5.5).

For a full list of references, see the article at https://bit.ly/35HeLko.
Named one of the 10 best hospitals for Cancer in the U.S.

At Cedars-Sinai, the dedication of our doctors and staff has made us one of the most recognized hospitals in the nation. We’re proud to have earned a place on U.S. News & World Report’s Best Hospitals Honor Roll. This recognition belongs to our entire team who shows up day after day, night after night, for all of Southern California.

Learn more about our cancer care: cedars-sinai.org/cancer
IMMUNOTHERAPY AGENTS HAVE demonstrated moderate clinical activity for patients with gynecologic cancers, but have failed to yield significant response rates in both the newly diagnosed and recurrent setting. Although pan-tumor indications provide options for some patients, further exploration of molecular subtypes may be the key to unlocking success in certain histologies, according to Ursula A. Matulonis, MD.1

In a presentation during the 38th Annual CFS® virtual conference, Matulonis, who is the chief of the Division of Gynecologic Oncology at Susan F. Smith Center for Women’s Cancers and Brock-Wilson Family Chair at Dana-Farber Cancer Institute, and a professor of medicine at Harvard Medical School, took stock of the role for immunotherapy agents in the treatment landscape for ovarian, recurrent/advanced endometrial, and recurrent/advanced cervical cancers.

IMMUNE CHECKPOINT INHIBITORS STRUGGLE IN OVARIAN CANCER

Investigators have found that adding immunotherapy to platinum chemotherapy in the up-front setting for patients with newly diagnosed disease does not show any benefit. This was exemplified in 2 clinical trials: JAVELIN Ovarian 100 (NCT02718417) and IMagyn050 (NCT03038100).

Specifically, patients enrolled in JAVELIN Ovarian 100 received either carboplatin, paclitaxel, and avelumab (Bavencio) with or without maintenance avelumab or chemotherapy alone. Those enrolled in IMagyn050 received either carboplatin, paclitaxel, and bevacizumab (Avastin) plus bevacizumab maintenance, or carboplatin, paclitaxel, atezolizumab (Imfinzi) and bevacizumab with bevacizumab and atezolizumab maintenance.

“When you add avelumab as a maintenance therapy, you actually see a worsening of outcomes,” Matulonis explained. Notably, JAVELIN Ovarian 100 investigators terminated the trial due to a lack of efficacy, demonstrated during the planned interim analysis. She added, “There is no improvement in progression-free survival nor observed overall survival benefit with the addition of avelumab or atezolizumab, respectively.”

Investigators have also examined the efficacy of immunotherapy agents in patients with recurrent disease. Matulonis pointed to data from 3 studies in which reported response rates were 15.0% (n = 20) for nivolumab (Opdivo; UMIN000005714), 9.6% (n = 125) for avelumab (JAVELIN Solid Tumor; NCT01772004), and 8.0% (n = 376) for pembrolizumab (Keytruda; KEYNOTE-100; NCT02674061).2−4 Although the response rate in patients treated with nivolumab was promising, patients treated with avelumab and pembrolizumab displayed only modest responses.

Further, data from the phase 3 NINJA trial (JapicCTI-153004) showed a small difference in median overall survival (OS) for single-agent nivolumab compared with chemotherapy in patients with platinum-resistant ovarian cancer (10.12 vs 12.09 months, respectively).5 Median progression-free survival (PFS) was not improved in those who received nivolumab (2.04 vs 3.84 months, respectively).

“There were higher risks of toxicities with chemotherapy, but the efficacy results do not support the general use of checkpoint inhibitors for recurrent platinum-resistant ovarian cancer,” Matulonis said.

“There are other trials ongoing, but we’re not making much headway with the use of immune checkpoint inhibitors in recurrent ovarian cancer,” she continued. “Some new strategies are really necessary.”

PAN-TUMOR APPROVALS PAVE A PATH FORWARD

The American Society of Clinical Oncology guidelines for germline and somatic tumor testing in epithelial ovarian cancer recommend that women with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing in order to detect mismatch repair deficiency (dMMR). Although dMMR is rare in high-grade serous ovarian cancer, it appears to occur more commonly in nonserous ovarian cancer, according to Matulonis.6

In 2017, the FDA approved pembrolizumab for patients with microsatellite unstable (MSI)-high and dMMR cancers. This was followed by the 2020 approval of the agent for the treatment of patients with tumor mutational burden (TMB)-high cancers (≥ 10 mutations/megabase).7

Although pan-tumor approvals with single-agent immune checkpoint inhibitors have demonstrated clinical activity in patients with dMMR or MSI-high cancer, navigating PD-1/PD-L1-targeted treatments remains an uphill battle. Various agents have shown reasonable response rates in patients with endometrial cancer, including dostarlimab (TSR 042), durvalumab (Imfinzi), pembrolizumab, and avelumab. Matulonis said that up to 30% of patients with endometrial cancer have dMMR or MSI-high disease. However, she indicated that there is an unmet need for patients with MMR-proficient disease.1

“Response rates are much lower, sometimes 0%, in MMR-proficient disease [with these agents, which] are not approved [in this indication],” she said. Notably, pembrolizumab is approved in combination with lenvatinib (Lenvima) for patients with MMR-proficient recurrent endometrial cancer.

“It’s important to remember the toxicities of this regimen. [The rate in] patients who had treatment-related adverse effects leading to steady drug discontinuation was 18.5% for both drugs,” Matulonis said. “About 9.3% of patients had to stop both drugs, around 15.7% of patients had to stop lenvatinib, and 13% had to stop pembrolizumab. Almost 64.8% of patients had to have some kind of
dose reduction of lenvatinib, so just remember that when you’re starting [the regimen].”

**IMMUNOTHERAPY FOR PD-L1–POSITIVE CERVICAL CANCER**

Data for patients with cervical cancer have shown benefit for those treated with a PD-1 inhibitor. In 2018, the FDA approved pembrolizumab for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (combined positive score, ≥ 1).2

Although the single agents have shown modest improvement, combination strategies provide a mixed bag of results. In a phase 2 study (NCT02921269), the combination of atezolizumab and bevacizumab failed to meet its primary end point and yielded an overall response rate (ORR) of 0% (n = 10).8

Investigators of CheckMate358 (NCT02488759) examined the combination of nivolumab and ipilimumab at 2 doses: 3 mg/kg nivolumab and 1 mg/kg ipilimumab, and 1 mg/kg nivolumab and 3 mg/kg of ipilimumab.9 In the first cohort, patients with no prior systemic treatments had an ORR of 31.6% (n = 19) and patients who were heavily pretreated had an ORR of 23.1% (n = 26). In the second cohort, those with no prior treatment had an ORR of 45.8% (n = 24) and those who were heavily pretreated had an ORR of 36.4% (n = 22).

In the first cohort, investigators noted a median PFS of 13.8 months (95% CI, 2.1-not reached [NR]) in patients who had not received prior treatment compared with 3.6 months (95% CI, 1.9-5.1) in those who had. The second cohort had a median PFS of 8.5 months (95% CI, 3.7-NR) and 6.8 months (95% CI, 3.5-17.2), respectively. Further, the duration of response was not reached in patients who had not received prior systemic therapy for relapsed or metastatic disease in both cohorts.

“Higher response rates were observed in patients who had no prior systemic treatments. The less heavily pretreated patients had better response rates,” said Matulonis. “There was some suggestion that response rates were higher in 1 mg/kg nivolumab and 3 mg/kg of ipilimumab, but this [study] was not meant to take a look at that.”

A notable development in combination therapy came in March 2020, when the FDA granted a fast track designation to the PD-1 inhibitor balstilimab and the CTLA-inhibitor zalifrelimab for the treatment of patients with relapsed or refractory metastatic cervical cancer. The combination showed durable responses in an all-comer, nonbiomarker-selected population of patients with refractory cervical cancer who progressed following prior platinum-based chemotherapy with or without bevacizumab.10

In data presented at the 2020 European Society for Medical Oncology Annual Congress, the combination demonstrated a 22% ORR (n = 143), with 8 complete responses and 23 partial responses. Further, data for single-agent balstilimab showed a 14% ORR, which included 3 complete responses and 20 partial responses. The drug’s manufacturer has initiated a rolling submission of a biologics license application to the FDA for balstilimab’s use in the treatment of patients with recurrent/metastatic cervical cancer.

---

**Hussain Discusses PARP Inhibition Progress in Metastatic Castration-Resistant Prostate Cancer**

BY DENISE MYSHKO

PAPR INHIBITORS HAVE EMERGED as a favorable therapeutic target in prostate cancer, said Maha H. A. Hussain, MBChB, at the 38th Annual CFS® virtual conference.

“It’s amazing how many clinical trials are ongoing with different PARP inhibitors. There are several phase 3 and phase 2 clinical trials looking at different disease settings,” said Hussain, who is the Genevieve E. Teuton Professor of Medicine in the Division of Hematology and Oncology, Department of Medicine, and deputy director at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University Feinberg School of Medicine.

“Prostate cancer is a very smart disease, and it has a significant intra- and interpatient heterogeneity and variability in its behavior…,” she said. “Clearly, whatever we do has to focus on the totality of the disease biology and individualized care.”

Targeted therapies have only just started to be approved for prostate cancer, said Hussain, a 2015 Giants of Cancer Care® award winner in genitourinary cancer. Two PARP inhibitors were approved in May 2020 to treat patients with metastatic castration-resistant prostate cancer (mCRPC): rucaparib (Rubraca), which received an accelerated approval, and olaparib (Lynparza), which was granted full approval.

The FDA approved rucaparib for patients with deleterious germline and/or somatic BRCA-mutated mCRPC based on findings from the single-arm, phase 2 TRITON2 study (NCT02952534). The trial enrolled 115 patients who had progressed following treatment with 1 to 2 lines of next-generation androgen receptor–directed therapy and 1 taxane-based chemotherapy. Results showed that the objective response rates (ORRs) for evaluable patients based on independent radiology review and investigator assessment were 43.5% (95% CI, 31.0%-56.7%; 27 of 62 patients) and 50.8% (95% CI, 38.1%-63.4%; 33 of 65 patients), respectively. ORRs were similar for patients with a germline or somatic BRCA alteration and for patients with a BRCA1 or BRCA2 alteration. Notably, investigators observed a higher prostate-specific antigen (PSA) response rate in patients with a BRCA2 alteration. The most frequent grade 3 or
higher treatment-emergent adverse event was anemia (25.2%).

Olaparib is indicated for patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene–mutated mCRPC who have progressed following prior treatment with enzalutamide (Xtandi) or abiraterone acetate (Zytiga). The approval was based on data from the phase 3 PROfound Study (NCT02987543), a trial of olaparib versus investigator’s choice of enzalutamide or abiraterone acetate. Patients were stratified into 2 cohorts: cohort A (n = 245) comprised patients with at least 1 alteration in BRCA1, BRCA2, or ATM, and cohort B (n = 142) comprised patients with at least 1 alteration in any of the other 12 prespecified genes. In updated published data, the median duration of overall survival in cohort A was 19.1 months with olaparib versus 14.7 months with control therapy (HR, 0.69; 95% CI, 0.50–0.97). In cohort B, the median duration of overall survival was 14.1 months with olaparib versus 11.5 months with control therapy.

Overall, patients tolerated the treatment well, with the most frequent high-grade adverse event being anemia.

“There are many lessons we have learned from PROfound,” said Hussain. “We have screened over 4000 patients internationally. The success rate with NGS [next-generation sequencing] testing, which was done on all patients, was 69%.”

Newly collected tissue, for example, had a higher success rate compared with archival tissue, but if archival tissue was used, samples collected less than 5 years prior to the trial had better success rates. Further, the success rate in tissue collected from metastatic disease was 63.7% compared with 56.3% in primary samples. This rate may be because of the higher cellularity and tumor content that is more often seen in the metastatic site, Hussain said (FIGURE 1).

“The critical part of tissue collection, which is something I think is [vital] when you are speaking with your radiologist if you’re doing a fresh biopsy, is that multiple core biopsies are necessary,” Hussain said. These samples should then be embedded into 1 formalin-fixed, paraffin-embedded block to maximize the likelihood of successful pathologic review.

FUTURE DIRECTIONS
Although these 2 trials and agents have broken through as therapeutic options, Hussain said continued research of PARP inhibitors is necessary. Questions remain about these therapies, especially concerning the best timing of administering them, their relation to other life-prolonging treatments, the sensitivity of the disease to PARP inhibitors and other treatments, tumor heterogeneity, and how to overcome mechanisms of resistance.

Investigators of the phase 2 CheckMate 9KD trial (NCT03338790) are exploring the efficacy of rucaparib in combination with nivolumab (Opdivo), docetaxel plus prednisone, or enzalutamide in patients with mCRPC. The trial is currently active, but not recruiting. Additionally, data from the phase 2 TRIUMPH trial (NCT03413995) will determine if rucaparib leads to the lowering of PSA levels in men with metastatic hormone-sensitive prostate cancer who have an inherited mutation in a gene involved in repairing DNA damage.

Olaparib is being explored both in combination therapy and as monotherapy across trials. “We developed a randomized clinical trial that is asking, if a patient has canonical HRR mutations, specifically in BRCA 1/2 or ATM, does it make a difference if they get olaparib, abiraterone acetate, or the combination [of olaparib, abiraterone, and prednisone],” Hussain said. The trial, BRCAAway (NCT03012321), is almost fully enrolled, she added.

Investigators of the phase 3 PROpel Study (NCT03732820) will evaluate the efficacy of olaparib in combination with abiraterone acetate alone as a first-line therapy for mCRPC. The planned subgroup analysis will include HRR gene status.

Other PARP agents being studied include niraparib (Zejula), talazoparib (Talzenna), and pampirib (BGB-290). Several studies are investigating niraparib, including as a monotherapy (Galahad; NCT02854436), in combination with apalutamide (Erleada) or abiraterone (BEDIVERE; NCT02924766), and in combination with radium-223 dichloride (Xofigo) (NiraRad; NCT03076203).

In addition, investigators are studying talazoparib in combination with enzalutamide (TALAPRO-2; NCT03395197) and in combination with avelumab (Bavencio) (JAVELIN PARP MEDLEY; NCT03330405), as well as examining pamiparib in combination with temozolomide (Temodar) in a phase 1 study (NCT03150810).

REFERENCES
Evaluating a Selective FGFR Inhibitor Treatment for Advanced Cholangiocarcinoma (CCA)
An investigational, targeted, oral, chemo-free agent

The Phase 3 PROOF Trial is evaluating the efficacy and safety of infigratinib (BGJ398), a targeted, oral, chemo-free agent, vs chemotherapy in patients with unresectable locally advanced or metastatic CCA with FGFR2 fusions.

Inclusion criteria*:

• Have histologically or cytologically confirmed unresectable locally advanced or metastatic CCA†

• Have written documentation of local laboratory or central laboratory determination of FGFR2 gene fusions/translocations from tumor tissue collected before treatment

Note: Molecular testing offered by the trial, if needed.

* Additional eligibility criteria apply.
† For adults 18 years and older.

QED is focused on developing infigratinib, a potent, selective tyrosine kinase inhibitor to treat FGFR-driven diseases.

Efficacy and safety of infigratinib in CCA have not been established. Infigratinib is not currently approved by the FDA or other health authorities.

To learn more, please contact us at:
PROOF301@QEDTx.com
QEDPROOFTrial.com

©2019 QED Therapeutics, Inc. All rights reserved. MRC007 10/19
HAVING PATIENTS GO ON drug holidays or intermittent therapy is a common strategy during treatment of prostate cancer and several other malignancies, whether to provide temporary relief from adverse effects (AEs) influencing quality of life (QOL), to prevent long-term health impacts, or to lessen drug resistance that would render the therapy ineffective. Now, however, the coronavirus disease 2019 (COVID-19) pandemic has made the decision to take a break from ongoing therapy more complicated and more urgent.

Before the pandemic, “there was a lot of anxiety from different patient groups” about interrupting their therapy, said Howard A. “Skip” Burris, MD, chief medical officer and president of clinical operations at Sarah Cannon Research Institute in Nashville, Tennessee, and a 2014 Giants of Cancer Care® award winner in the Drug Development category.

“I had some men who were older, in their 70s, who were worried about doing intermittent androgen therapy, and yet when COVID hit and they were more worried about coming to the clinic, they put themselves on a break,” Burris said in an interview with OncologyLive®. “I had women who were on maintenance trastuzumab [Herceptin] in remission for a long time who were worried about coming to the clinic, so they took their first break.”

The American Society of Clinical Oncology (ASCO) Survey on COVID-19 in Oncology Registry (ASCO Registry) is collecting data on how the epidemic is affecting the delivery of care and patient outcomes, including for those who paused treatment or switched therapies, noted Burris, who served as ASCO president from 2019 to 2020. “Everybody in the ASCO Registry has to be on treatment, either metastatic or adjuvant, or they have to have been within a year of completing therapies,” he said. “I think we’re going to learn a lot from these data.”

The data could prove illuminating in part because, as common as drug holidays are, their safety and efficacy varies in trials. Data are often contradictory, equivocal, or simply lacking for many scenarios, and it can be unclear why some patients benefit from therapy pauses while others experience progression.

Several research teams are now testing adaptive therapies that include holidays and dose modulation based on disease biomarkers or evolving tumor cell resistance, rather than uniform sequencing plans. Personalized schedules have shown promising results in preclinical and small clinical studies and may pave the way for more patients to safely take breaks from treatment.

Regarding the definition of a “drug holiday,” Burris said the term means different things to different people. It can mean giving maintenance therapy intermittently, such as stopping chemotherapy and continuing only a checkpoint inhibitor administered once every 3 weeks, or stopping therapy in favor of active surveillance when a patient appears to be in complete or partial remission.

However, it can be difficult to gauge whether a patient still has active disease, and he said that he’s eagerly following adaptive therapy trials and other research that aims to inform intermittent dosing strategies.
Drug Holidays

“For the individual patient with cancer and metastatic disease, we’re closer to treating them as if they had a chronic disease. We need to then start thinking about alternative approaches, whether it be drug holidays, sequencing therapies, or whatever the terminology is,” he said. “We’ve had enough success with these drugs, and we’ve got patients living longer but not yet cured.”

PROSTATE CANCER QUESTIONS

In prostate cancer, “tons of studies in the past [have been] done on intermittent androgen deprivation [IAD]. Those roundly failed,” said Jacob Scott, MD, DPhil, a radiation oncologist at Cleveland Clinic Taussig Cancer Center in Ohio who studies evolutionary oncology. “One schedule doesn’t fit every person, and it might even be that the schedule that works for patient X stops working for patient X in 6 months because the cancer has changed. So it’s really about trying to understand the dynamics of an individual person’s cancer from some observables that we have.”

IAD may be the most thoroughly studied use of drug holidays. Continuous androgen deprivation (CAD) is the standard therapy for metastatic hormone-sensitive prostate cancer, but the resulting drop in serum testosterone levels is associated with sexual dysfunction, risk of cardiovascular disease, loss of bone and muscle strength, cognitive effects, and other AEs.1

Stopping androgen therapy for some period of time to allow testosterone levels to rise again is an important option for many men, said Nicholas J. Vogelzang, MD, a clinical professor at University of Nevada School of Medicine in Las Vegas and a 2018 Giants of Cancer Care® award winner, and colleagues, including Vogelzang. Investigators found significantly better erectile function and mental health (P < .001 and P = .003, respectively) with intermittent therapy than with continuous therapy 3 months after randomization but not thereafter. Additionally, the overall incidence of grade 3 or 4 AEs was similar between the 2 therapeutic approaches: 30.4% for IAD and 32.7% for CAD.2

Across the study population, median overall survival (OS) was higher in the continuous group at 5.8 years compared with 5.1 years in the intermittent group, representing a 10% relative increase in the risk of death with intermittent therapy (HR for death with intermittent, adjusted for stratification factors, 1.10; 90% CI, 0.99-1.23). The results “failed to show that intermittent therapy was noninferior to continuous therapy with respect to survival,” the investigators wrote. Additionally, they noted, findings suggested that intermittent therapy could hold a 20% greater risk of death, but there were too few events to make a determination.2

Subsequent analyses have reached varying conclusions. A 2015 study of data from 15 trials found support for the noninferiority of IAD, no difference in OS for the 2 groups, and minimal differences in patients’ self-reported QOL, although there was some improvement in physical and sexual functioning with IAD.3

Another 2015 study, by Hussain, Vogelzang, and colleagues, examined findings from 7 phase 3 trials and concluded that none demonstrated survival superiority of IAD compared with CAD. The trials that found IAD was not inferior were based on wide, prespecified noninferiority margins that likely would not be considered comparable by doctors or patients, they wrote.4

Last year Hussain et al said findings from another meta-analysis showed the paradigm for IAD has “not lived up to expectations.”5 However, they noted that newer treatment regimens, such as CAD combined with docetaxel and abiraterone acetate (Zytiga) in patients with metastatic hormone-sensitive prostate cancer, have allowed patients with prostate cancer to live longer, making the impact of AEs and the need for deintensification strategies more prominent.

Other recent options include FDA approvals of the second-generation androgen receptor antagonists apalutamide (Erleada) and enzalutamide (Xtandi) in combination with androgen-deprivation therapy (ADT) in metastatic castration-sensitive settings and darolutamide (Nubeqa) plus ADT in nonmetastatic castration-resistant disease.6

Hussain and colleagues acknowledged that experienced clinicians recognize the benefits of IAD but that doctors and patients must understand its potential negative impact, especially given the lack of data on intermittent use of newer therapies.5

The trials examined in the recent meta-analysis used several thresholds for pausing ADT: after 6 months; when prostate-specific antigen (PSA) levels fall below 4 ng/mL or reach 1 ng/mL or lower; or when PSA decreases 80% or 90% below baseline levels.

Vogelzang said he looks for patients to possibly take a break after 18 months if their PSA is below 0.1 ng/mL. “When do you stop? The answer is, no one knows,” Vogelzang said. “I have arbitrarily taken the point that maybe 18 months is enough. That’s just my personal world view.”

EXPLORING ADAPTIVE DOSING

Investigators at Moffitt Cancer Center in Tampa, Florida, have tried to lengthen time to progression (TTP) by personalizing on- and off-treatment cycles in a way that slows the evolution of cellular resistance to ADT. Investigators developed a game theory model based on interactions of intratumoral subpopulations with testosterone.7 When therapy is administered continuously at the maximum tolerated dose (MTD), investigators theorize, there is a rapid expansion of resistant T cells, whereas adaptive dosing allows the responsive cell populations to recover (FIGURE).7,8

In a small trial, men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) were enrolled after they achieved a PSA reduction of 50% or greater with abiraterone as frontline therapy.8,9

H. A. Hussain, MBChB, a 2015 Giants of Cancer Care® award winner, and colleagues, including Vogelzang. Investigators found significantly better erectile function and mental health (P < .001 and P = .003, respectively) with intermittent therapy than with continuous therapy 3 months after randomization but not thereafter. Additionally, the overall incidence of grade 3 or 4 AEs was similar between the 2 therapeutic approaches: 30.4% for IAD and 32.7% for CAD.2

Across the study population, median overall survival (OS) was higher in the continuous group at 5.8 years compared with 5.1 years in the intermittent group, representing a 10% relative increase in the risk of death with intermittent therapy (HR for death with intermittent, adjusted for stratification factors, 1.10; 90% CI, 0.99-1.23). The results “failed to show that intermittent therapy was noninferior to continuous therapy with respect to survival,” the investigators wrote. Additionally, they noted, findings suggested that intermittent therapy could hold a 20% greater risk of death, but there were too few events to make a determination.2

Subsequent analyses have reached varying conclusions. A 2015 study of data from 15 trials found support for the noninferiority of IAD, no difference in OS for the 2 groups, and minimal differences in patients’ self-reported QOL, although there was some improvement in physical and sexual functioning with IAD.3

Another 2015 study, by Hussain, Vogelzang, and colleagues, examined findings from 7 phase 3 trials and concluded that none demonstrated survival superiority of IAD compared with CAD. The trials that found IAD was not inferior were based on wide, prespecified noninferiority margins that likely would not be considered comparable by doctors or patients, they wrote.4

Last year Hussain et al said findings from another meta-analysis showed the paradigm for IAD has “not lived up to expectations.”5 However, they noted that newer treatment regimens, such as CAD combined with docetaxel and abiraterone acetate (Zytiga) in patients with metastatic hormone-sensitive
Drug Holidays

The study group comprised 15 men who were off the drug for at least 3 months before it was restarted for PSA progression. After more than 11 months of follow-up, 7 of the 15 had completed at least 2 adaptive therapy cycles at data cutoff in January 2019.9 Investigators calculated that the median radiographic progression-free survival (rPFS) would be no less than 30 months (P = .0068, Fisher exact test). Investigators said that result compared favorably with the 16.5-month median rPFS in the COU-AA-302 trial (NCT00887198) of abiraterone plus prednisone versus placebo in mCRPC.5,6 The Moffitt trial also required much less of the drug, with patients using only 49% as much abiraterone as with continuous therapy.

Such adaptive strategies exploit competition between treatment-resistant and treatment-sensitive tumor cells. Rather than using a traditional MTD strategy that aims to eradicate as many cells as possible at the start, the adaptive therapy allows some sensitive cells to remain and “out compete” resistant cells, slowing their growth during treatment breaks. Although resistant cells eventually increase enough that the treatment fails, investigators say that in a number of cancers, this type of tumor control strategy extends TTP longer than MTD does.

“The crucial point here is, they’re doing dose modulation or holidays in response to how the tumor grows,” said Alexander Anderson, PhD, chair of the Integrated Mathematical Oncology department and senior member at Moffitt Cancer Center. “If you don’t see much growth or it doesn’t grow too quickly or return to the size it was within a period of time, they’re not treating or they’re continuing to deescalate the dose. When it eventually returns to the size it started at, that’s when they kick the treatment back in.”

UNIFORM DOSING HITS SNAGS

That personalized approach contrasts with previous drug-holiday trials that randomly assigned patients to uniform dosing schedules, not only in prostate but also breast, melanoma, colorectal, and other cancers.

Findings from one such trial were presented at the European Society for Medical Oncology Breast Cancer Congress 2019 in Berlin, Germany.10 The phase 3 STOP&GO trial (EudraCT 2010-021519-18; BOOG 2010-02) enrolled 420 patients with advanced HER2-negative breast cancer and randomized them to either 8 cycles of continuous chemotherapy or an intermittent schedule of 4 cycles, a break, and then 4 more cycles.

The combined median OS for patients receiving first-line therapy of paclitaxel plus bevacizumab (Avastin) or second-line treatment with capecitabine or nonpegylated liposomal doxorubicin was 20.3 months for those on intermittent treatment compared with 23 months for those on continuous treatment (HR, 1.93; 95% CI, 1.26-2.95).10 A separate analysis found that physical OOL declined more in the intermittent arm and that mental OOL improved slightly in both groups, but increased more in the continuous arm.11

Serial holidays in melanoma treatment were explored in a phase 2 trial (NCT02196181) presented at the American Association for Cancer Research Virtual Annual Meeting 2020. The trial enrolled 242 patients with advanced BRAF V600E/K-mutated disease. After receiving dabrafenib (Tafinlar) plus trametinib (Mekinist) for 8 weeks, 206 nonprogressing patients were randomized to continuous dosing with the combination or intermittent treatment on a 3-week-off, 5-week-on schedule. Median progression-free survival (PFS) was 9 months with continuous dosing versus 5.5 months with intermittent (P = .064). Median OS was 29.2 months in both groups (P = .93) at a median follow-up of 2 years.12

Intermittent therapies have also been studied as ways to improve OOL for patients with metastatic colorectal cancer (mCRC). The OPTIMOX1 trial (NCT01023633), for example, randomly assigned patients to 2 different regimens of leucovorin and fluorouracil with oxaliplatin (FOLFOX). Arm A received continuous standard FOLFOX4 every 2 weeks until progression; arm B received FOLFOX7, a simplified leucovorin and fluorouracil regimen with high-dose oxaliplatin, for 6 cycles, followed by 12 cycles without oxaliplatin, and then FOLFOX7 again.13

The 2 groups fared similarly: Median PFS was 9.0 months in arm A and 8.7 months in arm B, and median OS was 19.3 and 21.2 months, respectively. Arm B had somewhat fewer grade 3/4 toxicities (54.4% arm A vs 48.7% arm B). The investigators concluded that oxaliplatin can be safely stopped after 6 cycles in a FOLFOX regimen.13

A 2013 review of mCRC rechallenge strategies discussed OPTIMOX1 and several other trials that had treatment holidays of a sort, but the overall implications were unclear due to varying study designs and results. The studies included the phase 3 COIN trial (ISRCTN27286448), which tested preplanned treatment holidays in 1630 patients with advanced colorectal cancer.14 Patients were randomized to receive either a continuous oxaliplatin-fluoropyrimidine combination (arm A), continuous chemotherapy plus cetuximab (Erbitux; arm B), or intermittent chemotherapy (arm C).14

In comparing results from arms A and C, investigators found that patients in the per-protocol population who received continuous therapy had a median OS of 19.6 months (interquartile range [IQR], 13.0-28.1) versus 18.0 months (IQR, 12.1-29.3) for those who had intermittent treatment. In terms of AEs, those in the continuous therapy arm experienced lower rates of nausea and vomiting (2% vs 8%) than those on intermittent therapy, respectively, but higher rates of grade 3 or worse hand-foot syndrome (4% vs 3%) and peripheral neuropathy (27% vs 5%).13

In their review of multiple studies, Tonini et al concluded that the data do not clearly define an optimal role for a treatment holiday in which all therapy is paused and for chemotherapy-free intervals with maintenance. They did see the potential for a role for rechallenge therapy for fit patients in third-line or fourth-line mCRC treatment.

“Intermittent treatment could be an important strategy in management of [patients with] mCRC when there is not the purpose of gaining an important tumor shrinkage,” they wrote.14

Intermittent immunotherapy has also been studied. One small phase 2 trial (NCT03126331) used a partially personalized strategy. Fourteen patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy were treated with nivolumab (Opdivo) for 12 weeks. Of those, 5 achieved a 10% or greater reduction in
Drug Holidays

FUTURE STRATEGIES

Moving forward, investigators should seek to tailor therapy according to tumor composition rather than using one-size-fits-all schedules, holidays, and doses. Anderson and colleagues at Moffitt showed in a preclinical, mathematical modeling study.\(^{17}\)

They found that tumors made up of a mix of sensitive and resistant cells, such as breast cancers and melanomas, were best managed by an adaptive approach that exploits the fitness cost of resistance and cellular spatial dynamics. However, homogeneous tumors composed of sensitive cells, such as testicular cancer and some lymphomas, tend to respond better to MTD. Translating these findings to the clinic would require measuring initial variation in drug sensitivity using immunohistochemistry and then periodically assessing of tumor burden using systemic biomarkers, circulating tumor cells, cell-free DNA, or imaging, the investigators said.\(^{17}\)

Other preclinical studies by the Moffitt group showed how adaptive therapies could work in breast cancer. Investigators applied paclitaxel to cell lines of metastatic triple-negative and estrogen receptor (ER)–positive breast cancer and measured tumor response with MRI. After initial intensive therapy achieved tumor control, it was maintained with progressively smaller doses. In 60% to 80% of animals, no treatment was necessary for intervals as long as several weeks.\(^{18}\)

A subsequent study investigated anti-estrogen therapy in which ER-positive xenografts were treated with systemic tamoxifen and cycles of estrogen suppression and stimulation. Brief interruptions in drug administration provided equal tumor control while using up to 50% less drug and maintaining high expression levels of ER and lower levels of MDR1, a glycoprotein.\(^{19}\)

One focus of adaptive therapy research has been tyrosine kinase inhibitors (TKIs), which inevitably stop working as resistance is acquired. Studies have demonstrated that some patients with non–small cell lung cancer (NSCLC) benefit from retreatment with the same EGFR-targeted TKI after a holiday.\(^{20}\) However, preclinical work by Scott and colleagues revealed patterns or “maps” of collateral sensitivities that displayed cross-resistance to first-line ALK TKIs in ALK-positive NSCLC, including after drug holidays, suggesting other strategies might provide optimal results in second-line settings.\(^{21}\)

Another study tested resistance to a battery of drugs in Ewing sarcoma cells after chemotherapy and again found replicable patterns of sensitivity and resistance.\(^{22}\)

Due to the randomness of cell evolution, having sensitivity maps does not on its own allow predictions in individual patients, Scott said, adding that with his next study, of EGFR–positive lung cancer cells, he hoped to overcome that gap by gathering tumor genomic data linked to sensitivity patterns.

“Once you have that map, the underlying hypothesis is that it’s fundamental. Therefore, when a patient comes to you, you could biopsy their tumor, do next-generation sequencing, and then match that sequencing result up to your map of in vitro genotype-phenotype mapping.”

Those genetically informed maps could someday allow continuous therapy adjustments over the course of treatment, he said. That could prove useful not only during regularly scheduled care but also after unexpected breaks, such as those that have occurred during the COVID-19 pandemic. Patients would “come in and tell you, ‘Whoops, I took a month off,’ and you say, ‘OK, well, we need to reassess the state of the tumor,’ with the assumption that it has kind of wandered around evolutionarily a little bit. As soon as you know where it starts, you can calculate the future to a certain extent,” Scott said.

Burris noted that frequent next-generation sequencing testing is already technologically feasible but not practically accessible to many patients. “I’m hopeful that we will have price points around DNA sequencing,” he said. “That you could do sequential liquid biopsies, sequential blood-based sequencing, and try to see what patterns of resistance are emerging.”

For a full list of references, see the article at OncLive.com.
Adagrasib Shows Early Efficacy in KRAS G12C-Mutant NSCLC and CRC

by DENISE MYSHKO

ADAGRASIB (MRTX849), A NOVEL agent aimed at KRAS G12C mutations, has demonstrated early signs of efficacy in patients with advanced non–small cell lung cancer (NSCLC) and colorectal cancer (CRC) whose tumors harbor the alteration, raising hopes for a new therapy against a challenging oncogenic target.

The objective response rate (ORR) with adagrasib monotherapy was 45% and 17% in cohorts of patients with unresectable or metastatic NSCLC and CRC, respectively, who participated in the ongoing phase 1/2 KRYSTAL-1 trial (NCT03785249). The study is now enrolling patients into combination arms that will test adagrasib with pembrolizumab (Keytruda) or afatinib (Gilotrif) in NSCLC or with cetuximab (Erbitux) in CRC. Overall, KRAS is the single most frequently mutated oncogene in human cancers, but there are no approved therapies that directly inhibit its activity despite nearly 4 decades of research. Adagrasib is an oral small molecule targeted against a subset of KRAS mutations, KRAS G12C, which are associated with a poor prognosis and lack of response to standard treatments. KRAS G12C alterations occur in about 14% of lung adenocarcinomas, 3% to 4% of CRCs, and 1% to 2% of several other cancers.

“G12C inhibitors take advantage of novel biology that was discovered a few years ago that allows them to covalently bind to KRAS. This discovery opened up the possibility that one could develop drugs specifically for this subset of KRAS-mutant cancers, and clinically we are starting to see some activity,” said Pasi A. Jänne, MD, PhD, director of the Lowe Center for Thoracic Oncology, Belfer Center for Applied Cancer Science, and Chen-Huang Center for EGFR Mutant Lungs at Dana-Farber Cancer Institute in Boston, Massachusetts, in an interview with OncologyLive®.

Specifically, investigators discovered a new binding pocket amenable to therapeutic targeting on KRAS G12C proteins, explained Melissa L. Johnson, MD, associate director of the Lung Cancer Research Program at Sarah Cannon Research Institute in Nashville, Tennessee.

“It’s called the switch-II binding pocket, and it’s only on KRAS G12C proteins,” Johnson said. “Because of this discovery, a small molecule that binds covalently, selectively, and irreversibly was able to be developed which locks KRAS in an inactive configuration. In the past, because it was difficult to bind directly to the KRAS protein, the ways in which we tried to manipulate KRAS involved inhibition of downstream effectors. We’ve done that with some success but unfortunately, we had never found a truly viable strategy.”

**KRYSTAL-1 TRIAL DESIGN**

In the KRYSTAL-1 trial, investigators are evaluating adagrasib in 6 experimental arms, 3 as a single agent and 3 in combination with other therapies (FIGURE). After a dose escalation phase, they identified the recommended dose for adagrasib as 600 mg twice a day.

Adagrasib monotherapy is being tested in separate cohorts for patients with NSCLC, CRC, and other solid tumors. The trial will assess adagrasib in combination with pembrolizumab, a PD-1–directed immunotherapy, or afatinib, a pan-HER inhibitor, in patients with NSCLC; or with cetuximab, an EGFR antagonist, in patients with CRC.

“The combination of adagrasib with pembrolizumab is intended to answer the question of whether inhibiting the tumor cell growth and causing the death of the tumor cells with the KRAS G12C inhibitor and then reactivating the immune system with pembrolizumab would be an effective combination. Pembrolizumab is the standard of care in lung cancer,” said Jänne, a leading investigator for the KRYSTAL-1 lung cancer cohort.

The combinations with cetuximab and afatinib are intended to assess whether EGFR inhibitors can block other pathways the tumor uses in response to KRAS G12C inhibition. “We know if you inhibit KRAS gene G12C in some lung and colon cancers, the cancers will turn on EGFR signaling to bypass that inhibition. It’s a compensatory
pathway. If you block that compensatory pathway, you can potentially have a more effective therapeutic strategy,” Jänne said.

The trial seeks to enroll 391 patients at 56 study locations throughout the United States. The primary end points are ORR, pharmacokinetics (PK) evaluation, and safety. The secondary end points are establishing a maximum tolerated dose, evaluating the safety and tolerability in combination with other therapies, and assessing the PK of adagrasib oral formulations.

Enrollment is complete for the phase 2 cohort of adagrasib as a monotherapy for patients in second- and third-line NSCLC, according to Mirati Therapeutics, which is developing adagrasib. The company anticipates submitting a new drug application for accelerated approval in 2021 for this patient population.

It is also planning registration studies for adagrasib as a monotherapy and in combinations for earlier lines of therapy for patients with NSCLC and CRC.5

Additionally, Mirati has an agreement with Strata Oncology to broaden patient identification and enrollment for KRYS TAL-1.6 Trial investigators will use StrataNGS, a genomic profiling that analyzes DNA and RNA from advanced solid tumors.

EARLY ADAGRASIB FINDINGS

In October 2020, preliminary results from KRYS TAL-1 were detailed at the virtual Molecular Targets and Cancer Therapeutics Symposium hosted by the European Organisation for Research and Treatment of Cancer, the National Cancer Institute, and the American Association for Cancer Research. The findings showed that adagrasib was tolerable and elicited durable clinical activity in patients with previously treated KRAS G12C-mutant NSCLC and demonstrated promising activity for pretreated patients with CRC and other solid tumors with the aberration.1,2

As of August 30, 2020, 79 patients with previously treated NSCLC received 600 mg twice a day in the phase 1/1b or phase 2 cohort of the study, Jänne and colleagues reported. Patients included in the analysis had undergone a median of 2 prior lines of therapy (range, 1-9); all patients had previously received platinum-based chemotherapy and 92% had also been treated with a PD-1/PD-L1 inhibitor.1

Among 51 patients evaluable for clinical activity (14 from phase 1/1b; 37 from phase 2), the ORR was 45%, all partial responses (PRs), after a median follow-up of 3.6 months. The stable disease rate was 51%, for a disease control rate (DCR) of 96.1%. Among 14 evaluable patients in the phase 1/2b cohort who had longer-term follow-up, the ORR with adagrasib monotherapy was 43% (6 of 14 patients), with most patients (5 of 6) remaining on treatment at the time of data cutoff. Four of the 6 patients reported a duration of treatment longer than 11 months, although the median time on treatment was 8.2 months.

A preliminary analysis of trial participants with NSCLC with co-occurring mutations of KRAS G12C and STK11 showed an ORR of 64% (9 of 14 patients). Approximately 30% of patients with KRAS G12C-mutant NSCLC also have an STK11 mutation, and these co-occurring alterations are significantly correlated with poor clinical outcomes to immunotherapy and platinum-based chemotherapy regimens.3

Johnson and colleagues reported pooled data for patients with KRAS G12C-mutant CRC and other solid tumors. Patients in the CRC cohort had received a median of 4 prior lines of therapy (range, 1-9), whereas those with other malignancies had received a median of 2 lines (range, 1-5). Among patients with CRC, the ORR was 17% (3 of 18 patients). An additional 14 patients had stable disease, for a DCR rate of 94%. At the time of analysis, 67% (12 of 18 patients) remained on treatment.2

Among 6 evaluable patients with other solid tumors, confirmed PRs were reported in 1 patient with endometrial cancer, 1 with pancreatic cancer, 1 with ovarian cancer, and 1 with cholangiocarcinoma. All 6 patients remain on treatment.

Investigators conducted a safety analysis on pooled data from 110 patients who received adagrasib at the recommended dose, including participants in the NSCLC, CRC, and other tumor cohorts. Frequently reported treatment-related adverse events (TRAEs) of any grade included nausea (54%), diarrhea (51%), vomiting (35%), and fatigue (32%). Grade 5 TRAEs included pneumonitis in 1 patient and cardiac failure in 1 patient.1,2

“Across all the cohorts enrolled, the encouraging finding is that this drug is capable of resulting in responses, regardless of the tumor type,” Johnson said. “This is one of the first studies that has been able to show this for KRAS-mutant cancers. As a single agent, adagrasib appears to work well for patients with lung cancer. For patients with colorectal cancer, on the other hand, it may be part of a combination strategy.”

Johnson also pointed out that adagrasib has favorable bioavailability with a half-life of 24 hours. “All of those things are critical to developing a small molecule for the effective inhibition of an oncogene,” she said.

“In particular for KRAS-mutant colorectal cancer, these properties are important. We know that the KRAS protein regenerates or resynthesizes once every 24 hours and as the half-life of the drug is 24 hours, we are effectively inhibiting the KRAS protein throughout the dosing interval.”

She noted that this is important particularly for CRC when the KRAS-mutant protein is no longer inhibited. “That allows upregulation of the feedback-signal pathways mediated through EGFR. Colorectal cancer does tend to have been the most resistant to other RAS-directed therapies in the past.”

FURTHER RESEARCH

Moving forward, investigators will evaluate adagrasib in combination with pembrolizumab in patients with advanced KRAS G12C-mutant NSCLC in the phase 2 KRYS TAL-7 trial (NCT04613596).7

Additionally, in September 2020, Mirati announced a clinical collaboration with Boehringer Ingelheim to evaluate adagrasib in combination with BI 1701963, a SOSI::pan-KRAS inhibitor that blocks KRAS independent of mutation type in patients with lung and colorectal cancers.8
INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:
- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-medullary thyroid cancer (non-MTC)), and advanced or metastatic RET-mutant MTC.

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>85% ORR(^1)</strong></td>
<td><strong>64% ORR(^1)</strong></td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 17.5 months</strong></td>
</tr>
<tr>
<td>(95% CI: 12, NE); median follow-up: 7.4 months(^1,5)</td>
<td>(95% CI: 12, NE); median follow-up: 12.1 months(^1,5)</td>
</tr>
</tbody>
</table>

Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases\(^1\)

No patients received radiation therapy to the brain within 2 months prior to study entry\(^9\)

---

**Find RET. Find results on Retevmo.com.**

**Adverse Reactions and Laboratory Abnormalities**

- The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.

---

Retevmo\(^8\) is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates.

PP-SE-US-0397 11/2020 © Lilly USA, LLC 2020. All rights reserved.
Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia, or severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, hemorrhagic events can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage. Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryofoetal lethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeeding during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients: fatal adverse reactions which occurred in ≥1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were dry mouth (39%), diarrhea (37%), hypertension (18%), fatigue (15%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (13%).

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001 were AST increased (51%; 6%), ALT increased (45%; 9%), increased potassium (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of acid-reducing agents decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of strong and moderate CYP3A inhibitors increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of strong and moderate CYP3A inducers decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with CYP2C8 and CYP3A substrates increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in pediatric patients less than 12 years of age. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older.

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] < 50 mL/min, estimated by Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease.

Reduce the dose when administering Retevmo to patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.
RETEVMO™ (selpercatinib) capsules, for oral use
Initial U.S. Approval: 2020

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE
RETEVMO (selpercatinib) is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutated medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion-positive thyroid cancer who require systemic therapy who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.8% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 8%. The median time to first onset for increased AST was 4.1 weeks (range: 2 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALP and AST prior to initiating RETEVMO, every 1-2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity.

QT Interval Prolongation
RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in QTcF interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥ 3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

RETEVMO™ (selpercatinib) capsules, for oral use

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on data from animal reproduction studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryopathy and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final dose.

ADVERSE REACTIONS

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.

RETEVMO™ (selpercatinib) capsules, for oral use

Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
</tr>
</tbody>
</table>

Footnotes:

- Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.
- If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.
- Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.
- If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

Table 1 summarizes the adverse reactions in LIBRETTO-001.
Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
</tr>
<tr>
<td>Edema*</td>
<td>33</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
</tr>
<tr>
<td>Dyspepsia*</td>
<td>16</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence.
2 Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.
3 Fatigue includes fatigue, asthenia, malaise.
4 Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling face, eye swelling, peripheral swelling.
5 Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.
6 Headache includes headache, sinus headache, tension headache.
7 Includes cough, productive cough.
8 Includes dyspnea, dyspnea exertional, dyspnea at rest.

Increased Creatinine
In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents
Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with an H2 receptor antagonist or a locally acting antacid).

Strong and Moderate CYP3A Inhibitors
Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A Inducers
Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates
RETEVIMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVIMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVIMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval
RETEVIMO is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings from animal studies, and its mechanism of action, RETEVIMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVIMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternat exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women 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% to 4% and 15% to 20%, respectively.

Data

Animal Data
Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

Lactation

Risk Summary
There are no data on the presence of selpercatinib or its metabolites in human milk or on their 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 RETEVIMO and for 1 week after the final dose.

Table 2: Select Laboratory Abnormailties (≥20%) Worsening from Baseline in Patients Who Received RETEVIMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVIMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</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 675 to 692 patients.
Females and Males of Reproductive Potential

Based on animal data, RETEVIMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

RETEVIMO may impair fertility in females and males of reproductive potential.

Pediatric Use

The safety and effectiveness of RETEVIMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVIMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of RETEVIMO have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETEVIMO have not been established in pediatric patients for other indications.

Animal Toxicity Data

In 4-week general toxicology studies in rats, animals showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures > approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Mice pups also showed signs of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (>1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Geriatric Use

Of 702 patients who received RETEVIMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were > 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVIMO between patients who were ≥ 65 years of age and younger patients.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] > 30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease.

Hepatic Impairment

Reduce the dose when administering RETEVIMO to patients with severe (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVIMO-related adverse reactions in patients with hepatic impairment.

Rx only.

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

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA
Copyright ©2020, Eli Lilly and Company. All rights reserved.
SE HCP BS 08MAY2020

RETEVIMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08MAY2020
A Clinical Leader Reflects on New Era of Care at John Theurer Cancer Center’s Leukemia Division

by GINA MAURO

What are some key tactics you plan to enact in your new role?

I was very fortunate to step into a program that already had a strong foundation. I have been the interim chief for a couple of years now, and have been working to expand the program that Stuart Goldberg, MD, started. One of the backbones of what I’ve tried to build here, and what I hope to continue to build in the future, is this program that is very collaborative. The most important collaboration that I think we encounter on a day-to-day basis is our collaboration with the community. Hackensack University Medical Center’s John Theurer Cancer Center has always been a place where local, community providers can reach out to for input. Oncology is evolving at a record pace. I always say, ‘I’m not smart enough to be a community oncologist.’ Sometimes I feel that I can hardly keep up with leukemia, nevermind staying up to date on everything from colon cancer to CNS [central nervous system] tumors. I know a lot about a very little bit of oncology. We need to continue to prioritize our relationship with community providers, especially in our current era of oral oncology.

More and more patients are able to be treated [by community physicians] closer to home, so they don’t need to come here for every visit. I hope to continue to build this collaboration so that patients can come here for an opinion or their referring physician can call my cell phone, and we can work together to care for patients closer to home. That way, they’re plugged in, and we can also make sure that when we have a clinical trial available for them, we can get them on that study.

We would like to have a clinical trial for every patient, at every point during their treatment for AML.

As James K. McCloskey II, MD, begins the next chapter of his career as chief of the Division of Leukemia Hackensack Meridian John Theurer Cancer Center at Hackensack University Medical Center (JTCC), he is in awe of how much the institution—and the leukemia treatment paradigm overall—has evolved since he joined 7 years ago.

“Things are changing incredibly rapidly,” McCloskey reflected, “I’m just very grateful to be part of that.”

McCloskey, who will continue in his role as director of the Program for Myeloproliferative Neoplasms at JTCC, previously served as interim chief in the Division of Leukemia. Prior to joining JTCC, he was chief fellow in the Department of Hematology and Oncology at Georgetown University Hospital, where he also completed his residency.

With the armamentarium for patients with acute myeloid leukemia (AML) rapidly shifting, McCloskey’s time as chief will be anything but lackluster. “Seven years ago when I finished my fellowship at Georgetown University Lombardi Comprehensive Cancer Center, my mentor at the time, who was a senior lymphoma physician, asked me, ‘Why do you want to do leukemia? Leukemia hasn’t changed since I was a fellow.’ And I realized, when I was thinking about this today, that it has changed entirely in the past 7 years,” he said. “Since 2017, we’ve had 9 new drugs approved for acute myeloid leukemia [TABLE]. Seven of those were studied here in our division, and there have been 3 new therapies in acute lymphoblastic leukemia.”

In an interview with OncologyLive®, McCloskey discussed his goal of continuing to foster collaboration between JTCC and community physicians and boosting clinical trial options across hematologic malignancies, as well as holding down the fort during the coronavirus disease 2019 (COVID-19) pandemic.

### TABLE. Drug Indications in AML 1,2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midostaurin (Rydapt)</td>
<td>In combination with standard cytarabine and daunorubicin induction and cytarabine consolidation for the treatment of adult patients with newly diagnosed FLT3 mutation–positive AML</td>
</tr>
<tr>
<td>Gilteritinib (Xospata)</td>
<td>For adult patients who have R/R AML with the FLT3 mutation</td>
</tr>
</tbody>
</table>
| Ivosidenib (Tibsovo) | • For adult patients with newly diagnosed AML who are aged ≥ 75 years or who have comorbidities that preclude use of intensive induction chemotherapy  
  • For adult patients with R/R AML |
| Enasidenib (Idhifa) | For adult patients with R/R AML with an /DH2 mutation |
| Venetoclax (Venclexa) | In combination with azacitidine, or decitabine, or LDAC for patients with newly diagnosed AML who are aged ≥ 75 years or who have comorbidities that preclude use of intensive induction chemotherapy |
| Glastragib (Daurismo) | In combination with LDAC for patients with newly diagnosed AML who are aged ≥ 75 years or who have comorbidities that preclude intensive induction chemotherapy |
| Gemtuzumab ozogamicin (Mylotarg) | • For pediatric patients aged ≥ 1 month and adults with newly diagnosed CD33-positive AML  
  • For pediatric patients aged ≥ 2 years and adults with R/R CD33-positive AML |
| Cytarabine and daunorubicin (Vyxeos) | Liposomal combination for adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes |
| Azacitidine tablets (Onureg) | For continued treatment of patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy |

AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete blood count recovery; LDAC, low-dose cytarabine; R/R, relapsed or refractory.
Anything we can do to improve the outcomes of those patients—especially considering that many of these folks are older, frailler, and not necessarily able to receive an intensive conditioning regimen—would be very promising. We are excited to be participating in this study, which is accruing now.

For patients with AML, we also have the BioSight study [ELPIS; NCT03435848]. [This trial comprises] a new prodrug of cytarabine for patients who are older or not quite fit enough for induction. We have had a lot of success with that study; we are excited about outcomes with that agent as well. It will hopefully not only open up the possibility of more tolerable therapies for these patients, but it also might be the kind of backbone for future combination studies. We really do have a host of trials for almost every disease space.

### How would you describe your clinical approach?

The challenging thing in leukemia is that it’s not appropriate to take a one-size-fits-all approach. What I try to do is find the right therapy for each patient, based on their biology, their disease, and the characteristics of disease at presentation, but also their own personal goals. We have a lot of options. Part of the decision for [treatment] is: What does that patient want? What does quality of life mean [to them]? Where do they want to receive their therapy? What kind of support do they have at home? We try to consider all those things to find the right therapy for each patient who comes in the door.

There is another thing that I really do think is key to our success here. What is so unique is that we work so closely with our transplant program. When you talk to other providers, either larger or smaller institutions, it isn’t always so cohesive. Sometimes it feels as if [they have] very separate divisions. While we’re separated here, we really do work in tandem to try to make sure that from the day that I see [a patient], we’re planning the right initial therapy, considering the role of transplant, and starting that workup early, which is really crucial to potentially capturing that window during which a patient might be able to go to transplant.

That allows us to be a lot more successful. By having a transplant program across the hall, we are able to easily shave off a 30-day window for people undergoing induction to get that patient moving toward transplant.

### You’re stepping into this position in the midst of the COVID-19 pandemic. What adjustments has JTCC made during this time for patients?

It has been a crazy [8] months, to say the least. For us, when this pandemic hit, I remember, during all the [virtual] meetings, each division had a very different outlook on how this was going to impact them and how they were going to approach things.

For us, for the most part, especially if you consider acute leukemias, we really view these as oncologic emergencies. Our priority was to make sure that we did not allow for significant delays in care or access to treatment because these are often rapidly [progressing], and even fatal, hematologic malignancies. I am very proud of how our institution handled a pandemic; we never really shut down [the center]. Our doors were always open, we always maintained an inpatient floor, and the leukemia and transplant teams worked very closely to quickly manage protocols to help us improve our patients’ safety.

From just the first week that we had a patient identified [with COVID-19] in New Jersey, we adopted universal masking, which has clearly improved the safety of both our providers and our patients. We continue to screen patients on a regular basis in terms of symptoms or exposures before they get in the building. All patients are being screened prior to admission. Especially in the Division of Leukemia—knock on wood—we’ve had very few issues with COVID-19, and no nosocomial events. We have managed to stay open and provide care to patients safely.

### REFERENCES


Oncology Providers Face Rising Pressures From Payers Over Therapy Choices

by ANNE RUNYON

HISTORICALLY, INSURANCE COMPANIES have taken little action to manage oncology drugs and have left prescripting decisions largely up to provider preference, mostly because of the complexity and sensitivity of treating cancer.

It appears, however, that the companies are beginning to indirectly manage prescribing to better manage costs. Namely, they are shifting financial risk to providers and, in doing so, are trying to push providers to consider cost effectiveness, as well as the efficacy and safety of treatments. If providers are forced to consider cost to a greater extent, payers reason, they may begin to do more robust clinical and cost-effectiveness analyses to inform their decision-making.

The cost of oncology treatment is high and rising in the United States. For example, the monthly price of novel oncology drugs increased on average by 9% annually, and the average monthly cost of oncology drugs more than doubled between 2006 and 2015, from $7,103 to $15,535.1 This raises the question whether insurance companies will begin to employ new tactics to influence provider-prescribing decisions toward lower-cost treatment options.

To this end, Two Labs conducted a survey of 120 oncologists practicing in the United States to better understand the extent to which insurance companies are placing financial pressure on them and how this influences their prescribing decisions.2

As a follow-up, an oncologist at a large academic treatment center participated in a multidisciplinary panel that included representatives from an insurance company and from manufacturers of oncology medications.

INCREASING FINANCIAL PRESSURE

The survey findings suggest that across 6 major oncology indications—non-small cell lung cancer, chronic lymphocytic leukemia, breast cancer, colorectal cancer, acute lymphoblastic lymphoma, and diffuse large B-cell lymphoma—prescribers at large academic institutions believed that payers have increased the financial management of oncology therapies, making it more difficult to prescribe their first choice of therapy. (FIGURE 1).

In addition, the findings confirm that prescribers are feeling increased financial pressure. The participating oncologist, whom Two Labs is not identifying in this article, is aware of an increase in payer management in recent years, noting that she has had to change her first-choice medication about 20% of the time.

PATHWAYS OF CARE

Pathways of care are a new management tool that have emerged in recent years as an attempt to curtail the increasing costs of oncology drugs by recommending which ones to prescribe in early and late lines of therapies. Payers incentivize providers to follow pathways by either offering upside financial rewards for compliance or downside risks for deviating from recommendations.

The survey findings suggest that pathways of care often strongly recommend or mandate the use of certain high-cost drugs over others, for example, a PD-1 inhibitor such as Keytruda (pembrolizumab) over nivolumab (Opdivo) or ipilimumab (Yervoy).

Although in theory care pathways may be useful in standardizing care, noted the oncologist, in reality, each patient requires an individualized treatment approach. She has not seen any evidence that following such pathways leads to better patient outcomes.

FIGURE 1. KOL Perceptions of Payer Involvement in Academic Centers

FIGURE 2. How Are Insurance Companies Shifting Financial Risk?
and also suggests that pathways can quickly become dated and not accommodate the rapidly changing landscape in oncology. Initially, she was expected to adhere to pathways 70% of the time and there were only upside financial incentives. Then, adherence expectations increased to 80% and negative penalizations were introduced.

Another challenge for providers is that they must often juggle multiple pathways from different insurance companies, and in some cases from their institution as well. In some cases, providers juggle more than 3 pathways. The panel’s oncology provider handles multiple pathways. This causes her to choose the “least common denominator” treatment option, the one most likely to be covered on all pathways.

SHIFTING OF FINANCIAL RISK
The survey results suggest that payers are shifting financial risk to providers, with 73% of providers suggesting they agree or strongly agree with the statement that insurance companies have been shifting financial risk to their hospital system/practice. This trend is even more marked among prescribers at large academic centers, with 78% of the providers agreeing with the statement.

Of respondents who agreed or strongly agreed with the statement, 66% said that this caused them to reconsider prescribing decisions. The most common way providers experienced this is through bundled payments. Often, they also face cost penalties, and in some cases financial risk is shifted through upside bonuses (FIGURE 2).

The panel’s oncologist has also experienced the shifting of financial risk. Her institution participates in the Oncology Care Model (OCM), which was introduced in 2016 to help providers lower cost while improving quality of care. There are currently 138 practices and 10 payers participating in the OCM.¹

The oncologist notes that cost savings do not always capture the true value of care, as more effective therapies often have greater toxicities, which can be costly to manage.

Anne Runyon is a senior market access consultant at Two Labs, a pharmaceutical services company.

---

**Cyberattack Threat to Health Care Providers Is Growing**

**by TODD SHRYOCK**

WITH MUCH OF THE NATION’S health care infrastructure focused on coronavirus disease 2019 (COVID-19), the world’s hackers sense an opportunity. Cyberattacks are increasing, forcing hospitals and health care providers to divert precious resources to boosting security.

*Medical Economics* spoke with Matt Gyde, CEO of NTT Ltd Security Division, to discuss cybersecurity in health care, and how cybercriminals are using the pandemic to go after vulnerable facilities.

*Editor’s note: What follows is an excerpt from this conversation.*

**Why has there been an increase in the number of cyberattacks directed at health care institutions?**

Q

A

Different parts of the world have reacted differently to COVID-19, but a lot of what we saw was people starting to work from home. What we saw in the medical profession was an uptick in attacks against hospitals and facilities. One of the main reasons for that is that COVID-19 brought a lot of pressure onto the health care infrastructure as a whole. We published our Global Threat Intelligence report in May, and one key point is that the Internet of Things is being weaponized. As we’re making our lives easier by having everything connected, we’re also opening up to the abilities of the cyber criminals.

**Who are these hackers and what are they ultimately after?**

Q

A

Each group is after something different. Obviously, some groups are going after intellectual property, to see if they can get a step ahead without having to do the work. A lot of the cybercriminals are going after money right now. But some may target infrastructure, such as an x-ray machine or MRI, and put ransomware on it.

**How are hackers getting into health care systems?**

Q

A

It’s still sending an email to an individual and that person clicks the link. Then the hackers put a piece of malware on the infrastructure. Now, the interesting thing about malware, and going back to that Global Threat Intelligence report, is we’re actually seeing a lot more use of machine learning and artificial intelligence. The sophistication behind it is incredible.

**For ransomware, should you pay the ransom?**

Q

A

Ransomware is generally going to lock a device down so you can’t access it. My view on it is, no, you shouldn’t pay the ransom. I think that just encourages people to try again and potentially get some more money. But that’s from me in a non-critical situation. My view is that you should inform the authorities immediately.

**What do you see for the future of cybersecurity in health care?**

Q

A

The general trend that we’ve seen, not just in health care but across all the industries, is that attacks are increasing. The attackers are becoming more sophisticated. They’re going to be going after the same things: intellectual properties, people’s details, and money.

To read the entire story, please visit *Medical Economics* at https://bit.ly/3nKdET.
Biomarkers Drive ICIs in Colon Cancer

by CANDICE SCHWARTZ, MD; AND SHIKHA JAIN, MD

IN THE PAST DECADE, immunotherapy has been incorporated into the standard of care for many malignancies. Agents have shown efficacy in malignant melanoma, kidney cancer, and non–small cell lung cancer, and investigators are examining the efficacy of checkpoint inhibitors in less immunogenic tumors such as colon cancer, particularly in tumors with high microsatellite instability (MSI-H) and deficient mismatch repair (dMMR) genes.

The DNA MMR genes MLH1, MSH2, MSH6, and PMS2 are involved in correcting errors that occur in DNA replication. If these genes are deficient, the cells are unable to correct errors and they accumulate mutations that ultimately lead to malignant potential. Deficiency in these MMR genes is MSI or dMMR, and tumors with heavily mutated MMR genes are identified as MSI-H. Testing for MSI can be done by immunohistochemistry that stains for tumor expression, or polymerase chain reaction alone or within a next-generation sequencing panel.1,2

MSI/dMMR mutations can be somatic or germline mutations and testing for them has been part of the standard of care for patients with colon cancer since around 2013.3 The genes with germline mutations are present in familial colon cancer syndromes such as hereditary nonpolyposis colorectal cancer, or Lynch syndrome, which makes up approximately 2% to 4% of all colon cancer diagnoses. Therefore, if MSI/dMMR is detected, it has implications for the patient’s treatment and prognosis as well as for the patient’s family members, who may have the same mutations.1,3

Patients with MSI-H/dMMR colon cancer typically present with lower-stage disease and have a better prognosis. The availability of mutational status at diagnosis helps to determine if adjuvant therapy would benefit patients with stage II colon cancer. If a patient presents with stage II MSI-H colon cancer, the prognosis is better and clinicians typically do not recommend adjuvant therapy. Alternatively, patients with stage II microsatellite stable colon cancer have a less favorable prognosis and, in certain cases, clinicians recommend adjuvant treatment with a fluorouracil (5-FU)–based therapy.1

Until recently, MSI-H/dMMR metastatic colon cancer was treated with standard cytotoxic 5-FU–based chemotherapy plus VEGF or EGFR inhibitors depending on the tumor mutational status. In 2017, data from the CheckMate 142 trial (NCT02060188) showed that the anti–PD-1 agent nivolumab (Opdivo) alone or nivolumab plus the anti–CTLA-4 agent ipilimumab (Yervoy) could be used as a second-line therapy in patients with metastatic colon cancer not believed to be candidates for intensive chemotherapy and who had not received prior immunotherapy agents, and whose cancer was MSI-H.

Results from the phase 2 study demonstrated an objective response rate (ORR) of 60%, a 12-month progression-free survival (PFS) rate of 77%, and an overall survival (OS) rate of 83% with the combination of nivolumab and ipilimumab.4,5 In addition, results from KEYNOTE-164 (NCT02460198) showed the anti–PD-1 agent pembrolizumab (Keytruda) to be an effective subsequent therapy in metastatic MSI-H/dMMR colon cancer. The ORR was 33%, and the 12-month OS rate was 76% for patients who had received more than 1 prior line of therapy.6 Neither of these studies compared immunotherapy with standard of care. Immunotherapy did not show efficacy in patients with metastatic colon cancer that was MSI-low or with proficient MMR genes.

Until this year, there were minimal data to support immune checkpoint inhibitors as first-line therapy for patients with MSI-H/dMMR metastatic colon cancer. KEYNOTE-177 (NCT02563002) was a multicenter, open label, randomized control trial that evaluated pembrolizumab versus standard of care with 5-FU–based therapy plus bevacizumab (Avastin) or cetuximab (Erbitux) for metastatic MSI-H/dMMR colon cancer. The study findings showed a PFS of 55% with pembrolizumab versus 37% with chemotherapy at 12 months, and 48% versus 19%, respectively, at 24 months.

Investigators did not report OS as the study is ongoing; however, 83% of patients who received pembrolizumab continued to show response to therapy at 24 months. Patients tolerated pembrolizumab better than chemotherapy, in addition to its being more efficacious.7 On June 29, 2020, the FDA approved pembrolizumab for first-line therapy for patients with metastatic MSI-H/dMMR colon cancer.8

The MSI-H/dMMR subset of patients with colon cancer is a special population that requires a nuanced approach to determine therapy. Immunotherapy with checkpoint inhibitors has a role in the treatment of these patients, specifically in those with metastatic disease. However, given that MSI-H/dMMR colon cancer has a unique tumor biology, immunotherapy may have a role in local disease as well. Studies are evaluating the efficacy of immunotherapy in both the adjuvant and neoadjuvant settings, as well as the efficacy of immunotherapy plus chemotherapy in this patient population. As investigators gather more data, it is likely that the role of immunotherapy will continue to extend into the other stages of colon cancer.
Overcoming Clinical Challenges Associated With TP53-Mutant MDS, AML

by RACHEL NAROZNIAK, MA

TP53-MUTANT MYELODYSPLASTIC syndromes (MDS) and acute myeloid leukemia (AML) represent a molecularly distinct, poor-risk patient subgroup frequently associated with complex karyotypes, high propensity for relapse, and inferior overall survival (OS).1,2

Across TP53-altered MDS and AML, standard therapies for wild-type disease have been of minimal benefit, but a wave of investigational agents currently in development offers promise for patients with TP53-altered malignancies, which affect 8% to 12% and 5% to 10% of patients with MDS and AML, respectively.1,3 In contrast with wild-type, FLT3-, and IDH1/2-mutant MDS and AML, at present, no agents are indicated specifically for TP53-mutant disease.4

TP53 gene mutations or chromosome 17 loss resulting in TP53 deletion impair function of the TP53 tumor suppressor protein, which regulates DNA repair and cell division.5 TP53 mutations are the most common genetic alteration in oncology, presenting in approximately 50% of all invasive malignancies, and are the most powerful negative prognostic covariate in hematological cancers specifically.6

CLINICAL FEATURES OF MDS/AML

While the tendency is to think about MDS and AML as 2 different entities, the clinical features of TP53-mutant MDS and AML frequently overlap, according to Guillermo Garcia-Manero, MD, professor, chief of the Section of Myelodysplastic Syndromes, and deputy chair of Translational Research in the Department of Leukemia in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston. “The characteristics of patients with AML with a TP53 mutation are very, very similar to those of patients with high-risk MDS with the same molecular and cytogenetic characteristics,” Garcia-Manero said in an interview with OncologyLive®.

To be classified as MDS, disease must meet 1 of the following decisive criteria: dysplasia (≥ 10% in 1 or more of the 3 major bone marrow lineages), a blast count of 5% to 19%, or an observable MDS-associated karyotype, such as deletion 5q (del[5q]), del(20q), +8, and or -7/del(7q).1 Notably, del(5q) is the most commonly observed aberration in complex karyotypes.7 Whether the chromosomal abnormality is isolated or part of a complex karyotype in MDS or AML, del(5q) is strongly associated with concomitant TP53 mutations.1 Existing evidence has shown that TP53 mutations are predictors of poor outcomes with lenalidomide
Precision Medicine in ONCOLOGY® | LEUKEMIA

(Revlimid) in higher-risk patients with MDS and del(5q).1,8 Lenalidomide was approved in December 2005 for patients with transfusion-dependent anemia to low- or intermediate-1-risk MDS associated with a del(5q) abnormality with or without additional cytogenetic aberrations.9

Diagnoses of AML are generally made in the presence of 20% or more blasts in the marrow or peripheral blood, per the 2016 World Health Organization classification of AML, but diagnoses can still be made when blasts below 20% are seen in patients with recurrent cytogenetic abnormalities created by reciprocal translocations (t) or inversions (inv) such as t(15;17), t(8;21), t(16;16), or inv(16).2 However, the phenotypical similarity of TP53-mutant MDS and AML has led the field to perceive bone marrow blast percentage as an arbitrary mode of distinction, Garcia-Manero said. Further, many clinicians now view these 2 molecularly specific malignancies as “a homogeneous disease entity,” according to Hunter et al.3

TP53-altered MDS and AML are jointly associated with 3 main characteristics: low response to chemotherapy, chromosomal complexity, and dismal prognosis.3,6 “Finding this mutation is very important to treatment selection because we tend to use lower-intensity approaches that are often better tolerated and more effective than conventional higher doses of chemotherapy,” Garcia-Manero said. “We see that patients with this mutation are typically more sensitive to lower-intensity type of chemotherapy, such as hypomethylating agents.”

Hypomethylating agent (HMA) therapy is the standard of care (SOC) for patients with higher-risk MDS. However, TP53-mutant disease treated with HMAS infrequently achieves durable clonal suppression and typically has poor OS.4 The efficacy of standard treatment is commensurately lacking in AML. For decades, induction chemotherapy with cytotoxic agents, including anthracyclines and cytarabine, has been the therapy with cytotoxic agents, including anthracyclines and cytarabine, has been the standard of care (SOC) for patients with AML who are healthy enough to receive systemic treatment.3

However, TP53 mutations, which confer resistance to cytotoxic therapy, strongly correlate with inferior responses to induction chemotherapy. The complete response rate for TP53-mutant, induction chemotherapy-treated AML is from 20% to 40% with high relapse rates; median OS ranges from 4 to 9 months. Despite minimal responses and short survival, patients with TP53-altered AML tend to fare even worse than those who received standard systemic therapy, indicating that SOC treatment should still be considered for these patients, despite the therapeutic prognostic trends observed in the presence of a TP53 mutation.5

Beyond HMAs and chemotherapy, TP53 alterations also complicate the pursuit of allogeneic hematopoietic stem cell transplantation (allo-HSCT).3,6 Across de novo MDS and therapy-related MDS, TP53 is the only somatic gene mutation to predict not only inferior OS but also suboptimal benefit from allo-HSCT.9 Poor long-term outcomes seen with allo-HSCT in TP53-mutant AML have discouraged its use in this patient subgroup, with available data demonstrating posttransplant relapse rates of 40% and 50% at 6 months and 100 days after allo-HSCT, respectively.3

“The rate of relapse is significantly higher in patients with TP53 mutations. This is an important point because the toxicity [as a result of the transplant] could be potentially severe. When you [perform transplants in] patients with TP53 mutations with the standard of care, the relapse rate posttransplant is also very, very high, which suggests that we’re not just talking about resistance. Perhaps the TP53 mutation affects the stem cell-like part of the disease that is very difficult to control with chemotherapy,” Garcia-Manero said.

TP53-mutant MDS and AML are also marked by chromosomal complexities, including complex karyotype (CK), which refers to the presence of 3 or more cytogenetic abnormalities. CK is regarded as a highly adverse prognostic marker that is identified in approximately 10% of MDS diagnoses and has been associated with MDS progression to AML and inferior OS.6,11 TP53 mutations are frequently found in tandem with a CK in MDS and AML and are associated with the worst prognoses when they co-occur.4 “Because the TP53 gene has a role in maintaining the integrity of the genome, when the function of the gene is disrupted, it’s not uncommon to see multiple chromosomal aberrations that are associated with poor prognosis and resistance to therapy,” Garcia-Manero said.

**Fast Facts**

**TP53-Mutant MDS/AML**

- TP53 mutations affect 8% to 12% and 5% to 10% of MDS and AML diagnoses, respectively.
- The main clinical features of TP53-mutant MDS/AML are poor response to cytotoxic chemotherapy, poor prognoses, and chromosomal complexities.
- Median OS for TP53-mutant AML after standard chemotherapy is 4 to 9 months.
- Median OS for TP53-mutant MDS is 6 to 12 months.
- High rates of relapse are seen after treatment, particularly allo-HSCT.

**SURMOUNTING RESISTANCE, POOR RESPONSE**

Eprenetapopt (APR-246), an experimental small molecule manufactured by Aprea Therapeutics, Inc and magrolimab (formerly Hu5F9-G4), an anti-CD47 monoclonal antibody developed by Gilead Sciences, Inc, are 2 agents under investigation for TP53-mutant MDS and AML.5,10 “Eprenetapopt is a drug that binds to the TP53 protein and seems to be stabilizing its function. Early reports from clinical trials here in the United States and Europe are showing a high response rate with eprenetapopt in combination with decitabine,” Garcia-Manero said.

Eprenetapopt reactivates mutant TP53 proteins by restoring wild-type TP53 conformation and function to induce programmed cell death in patients with TP53-altered disease.3 The agent’s actionability in TP53-mutant MDS is being tested in an ongoing randomized phase 3 trial (NCT03745716) of frontline eprenetapopt with azacitidine (Vidaza) versus azacitidine alone in 154 patients.12
The pivotal study was initiated after eprenetapopt showed encouraging activity with an acceptable safety profile when coadministered with azacitidine in an earlier-stage trial. Data from the phase 1b/2 study (NCT03072043) that provided the impetus for the phase 3 investigation demonstrated the capacity of the eprenetapopt-containing regimen to induce high response rates across subpopulations. The overall response rate (ORR), assessed by 2006 International Working Group criteria for MDS, was 87% among the 45 patients evaluable for response. When stratified by MDS/AML and MDS/myeloproliferative neoplasm, the ORR was 88% and 75%, respectively. More than half of patients in the general population (53%) experienced a complete response (CR); 61% of the 33 patients with MDS achieved a CR. Further, a TP53 mutation, which was identified in 62% of enrolled patients, was predictive for a higher CR rate (69% vs 25%; \( P = .006 \)) with a trend for higher ORR (93% vs 75%; \( P = .17 \)). The study enrolled 55 patients with higher-risk MDS, MDS/myeloproliferative neoplasm, or oligoblastic AML who had not previously received an HMA. Like eprenetapopt, which currently holds FDA breakthrough therapy, fast track, and orphan drug designations in MDS, magrolimab is also “showing very significant activity in TP53-mutant MDS when combined with decitabine,” said Garcia-Manero. “It’s possible that at some point maybe next year, we will have results for these 2 compounds, which could potentially improve cure rates in this group of patients.”

The potential viability of magrolimab in the TP53-altered MDS/AML treatment landscape is supported by phase 1b data (NCT03248479) demonstrating the tolerability and durability of the first-in-class therapy tolerability when added to azacitidine. Magrolimab exerts its anticancer activity by targeting CD47, an immune checkpoint on the surface of macrophages that is overexpressed in myeloid malignancies. Efficacy data presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program showed that the combination induced the same best ORR (75%) in the subgroup of 12 patients with TP53-mutant AML and a separate subgroup of patients with TP53-mutant MDS (n = 4). Forty-two percent of patients in the AML cohort and 50% of patients in the MDS group achieved a CR. After a median follow-up of 8.8 months and 7.0 months in the AML and MDS subgroups, respectively, the estimated 6-month survival was highest among patients with MDS (91% vs 100%).

“The follow-up is not that long, so we don’t know the durability of these responses and the impact on overall survival, but we believe that these are very active compounds that could be used to treat patients with these diseases before and after transplant,” Garcia-Manero said.

The phase 1b data have since led the FDA to grant magrolimab a breakthrough therapy designation for patients with newly diagnosed MDS.

NEW FRONTIERS FOR TP53-MUTANT MDS/AML
If respective, ensuing trials of eprenetapopt and magrolimab confirm the benefit seen in earlier-stage studies, the TP53-mutant MDS and AML armamentarium could gain the first FDA-approved therapies indicated specifically for TP53-altered disease. It is not unreasonable to speculate that either experimental agent could enrich not only the treatment portfolio but also combination strategies in this space, Garcia-Manero said.

“It’s likely that these compounds could be combined with hypomethylating agents and with other drugs like BCL-2 inhibitors such as venetoclax [Venclexta], so we may see triplets of these drugs that could be quite active,” he observed.

If approved, eprenetapopt and magrolimab could later become critical components of a concept that Garcia-Manero and colleagues refer to as “total therapy,” which involves improving pretransplant treatment to increase the response rate, propelling more patients to allo-HSCT, and administering posttransplant therapy in a manner akin to maintenance treatment that will “hopefully result in improved outcomes,” Garcia-Manero said. “We’re starting to think a lot about how to implement these kinds of therapies after transplant.”
IF SHE RESPONDS TO CHEMOTHERAPY

ZEJULA is the only once-daily, oral, first-line maintenance monotherapy approved for advanced ovarian cancer in complete or partial response to platinum-based chemotherapy, regardless of biomarker status1-3

Indication
ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in ≥10% of all patients who received ZEJULA in PRIMA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia was reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders,
YOU RESPOND WITH ZEJULA¹

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS¹⁴

OVERALL POPULATION

38% REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH

MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR 0.62; 95% CI, 0.50-0.76) P<0.0001

Study Design: PRIMA, a randomized double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of once-daily ZEJULA versus placebo (2:1) in 733 women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to first-line platinum-based chemotherapy. The primary endpoint was a hierarchical calculation of PFS: first in patients with HRd tumors and then in all patients. PFS was measured from time of randomization to time of disease progression or death. At the time of PFS analysis, limited overall survival data were available with 11% deaths in the overall population.¹⁴

Important Safety Information (continued)

e specially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Embryo-Fetal Toxicity and Lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

The most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia, (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).


¹L, first-line; CI, confidence interval; CR, complete response; HR, hazard ratio; HRd, homologous recombination deficient; PFS, progression-free survival; PR, partial response.

Visit ZEJULA.COM/HCP¹ to explore the PRIMA data

Trademarks are property of their respective owners.

©2020 GSK or licensor. NRPJRNA200007 August 2020
Produced in USA.

Please see Brief Summary on the following pages.
Do not start Zejula until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 3). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue Zejula, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) of full prescribing information).

5.3 Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with Zejula.

In PRIMA, Grade 1/2 hypertension occurred in 6% of Zejula-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range 1 to 531 days) and with a median duration of 12 days (range 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 1/2 hypertension occurred in 5% of Zejula-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range 4 to 504 days) and with a median duration of 15 days (range 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUASARA, Grade 1/2 hypertension occurred in 5% of Zejula-treated patients with a median time from first dose to first onset of 15 days (range 1 to 316 days) and with a median duration of 7 days (range 1 to 118 days). Discontinuation due to hypertension occurred in <2% of patients.

Monitor blood pressure and heart rate at least weekly for the first two months, monthly for the first year and periodically thereafter during treatment with Zejula. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the Zejula dose, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information). Due to the potential risk to the fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of Zejula (see Use in Specific Populations (8.1, 8.3)).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labelling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia
- Bone Marrow Suppression (see Warnings and Precautions (5.2))
- Cardiovascular Effects (see Warnings and Precautions (5.3)).

6.1 Clinical Trials Experience

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

The most common adverse reactions of all grades in >10% of 1811 patients who received Zejula in the pooled PRIMA, NOVA and QUASARA trials were nausea (65%), thrombocytopenia (65%), anemia (56%), fatigue (55%), constipation (49%), musculoskeletal pain (36%), abdominopelvic pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (22%), leukopenia (21%), insomnia (21%), headache (21%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), distress (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of Zejula for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 729 patients received niraparib or placebo. Among patients who received Zejula, the median duration of treatment was 11.1 months (range 0.3 to 29 months).

### Table 1. Adverse Drug Reactions Reported in ≥10% of All Patients Receiving Zejula in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zejula</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nausea</td>
<td>39</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
</tr>
<tr>
<td>Renal and Urological Disorders</td>
<td>0.3%</td>
</tr>
<tr>
<td>Acute Kidney Injury*</td>
<td>0.2%</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6%</td>
</tr>
</tbody>
</table>

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

---

**Zejula (niraparib) capsules, for oral use**

*The following is a brief summary only; see full prescribing information for complete product information available at www.ZEJULA.com.*

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

Zejula is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who are in a complete or partial response to first-line platinum-based chemotherapy.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

Zejula is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who have achieved a complete or partial response to platinum-based chemotherapy.

1.3 Treatment of Advanced Ovarian Cancer After Three or More Chemotherapies

Zejula is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal carcinoma who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status, defined by either:

- a deleterious or suspected deleterious BRCA mutation, or
- genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

Select patients for therapy based on an FDA-approved companion diagnostic for Zejula.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received Zejula monotherapy in clinical trials. In 785 patients treated with Zejula in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with Zejula in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.5 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue Zejula if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

Hematologic adverse reactions (thrombocytopenia, anemia, and neutropenia) have been reported in patients treated with Zejula.

In PRIMA, the overall incidence of Grade 3 or 4 thrombocytopenia, anemia and neutropenia were reported, respectively, in 35%, 31%, and 21% of patients receiving Zejula. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of Zejula based on baseline weight or platelet count, Grade 3 or 4 thrombocytopenia, anemia and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving Zejula. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. In NOVA, Grade 3 or 4 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving Zejula. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. In QUASARA, Grade 3 or 4 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving Zejula. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 1% of patients.
### Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEULA in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA N=169</td>
<td>Placebo N=244</td>
</tr>
<tr>
<td>ZEULA N=169</td>
<td>Placebo N=244</td>
</tr>
</tbody>
</table>
- Decreased hemoglobin: 87/66 vs 29/1
- Decreased platelets: 74/13 vs 37/0
- Decreased leukocytes: 71/16 vs 9/0
- Increased glucose: 65/57 vs 3/3
- Decreased neutrophils: 66/25 vs 23/1
- Decreased lymphocytes: 51/29 vs 7/3
- Increased alkaline phosphatase: 46/21 vs 1/0
- Increased creatinine: 40/23 vs 0/0
- Increased magnesium: 36/34 vs 1/0
- Increased aspartate aminotransferase: 35/17 vs 1/0
- Increased alanine aminotransferase: 29/17 vs 2/1

### Table 3: Adverse Reactions Reported in ≥10% of Patients Receiving ZEULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA N=169</td>
<td>Placebo N=244</td>
</tr>
<tr>
<td>ZEULA N=169</td>
<td>Placebo N=244</td>
</tr>
</tbody>
</table>
- Blood and Lymphatic System Disorders
  - Thrombocytopenia: 54/5 vs 21/1
  - Anemia: 40/28 vs 23/1
  - Neutropenia: 36/8 vs 15/1
  - Leukopenia: 28/11 vs 5/0
- Gastrointestinal Disorders
  - Nausea: 59/11 vs 1/1
  - Constipation: 31/13 vs 1/1
  - Vomiting: 17/9 vs 0/1
- General Disorders and Administration Site Conditions
  - Fatigue: 44/36 vs 3/0
- Metabolism and Nutrition Disorders
  - Decreased appetite: 19/5 vs 1/0
- Nervous System Disorders
  - Headache: 20/7 vs 9/1
  - Dizziness: 14/13 vs 0/0
- Psychiatric Disorders
  - Insomnia: 21/14 vs 0/0

### Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA N=169</td>
<td>Placebo N=244</td>
</tr>
<tr>
<td>ZEULA N=169</td>
<td>Placebo N=244</td>
</tr>
</tbody>
</table>
- Decreased hemoglobin: 81/70 vs 21/0
- Decreased leukocytes: 70/36 vs 6/0
- Decreased platelets: 63/15 vs 18/0
- Increased glucose: 63/56 vs 2/1
- Decreased neutrophils: 60/27 vs 15/0
- Decreased lymphocytes: 52/30 vs 5/4
- Increased alkaline phosphatase: 43/17 vs 1/0
- Decreased creatinine: 43/17 vs 1/0
- Increased aspartate aminotransferase: 31/19 vs 1/0
- Increased alanine aminotransferase: 28/15 vs 2/2

### Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEULA in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>ZEULA N=367</td>
<td>Placebo N=179</td>
</tr>
</tbody>
</table>
- Blood and Lymphatic System Disorders
  - Thrombocytopenia: 61/5 vs 29/0
  - Anemia: 50/7 vs 25/0
  - Neutropenia: 30/6 vs 20/2
  - Leukopenia: 17/8 vs 5/0

### Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEULA in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>ZEULA N=367</td>
<td>Placebo N=179</td>
</tr>
</tbody>
</table>
- Decrease in hemoglobin: 85/56 vs 25/0
- Decrease in platelet count: 72/21 vs 35/0
- Decrease in WBC count: 66/37 vs 7/0
- Decrease in absolute neutrophil count: 59/25 vs 21/2
- Increase in AST: 26/33 vs 1/0
- Increase in ALT: 28/7 vs 1/0

*Note: Number of patients, WBC=white blood cells, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase*
Treatment of Advanced Ovarian Cancer After Three or More Chemotherapies

The safety of ZEJULA monotherapy 300 mg once daily has been studied in QUADRATA, a single-arm study in 485 patients with recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range 0.03 to 32 months). For the indicated QUADRATA population, the median duration was 4 months (range 0.1 to 30 months).

Fetal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >1% of patients were small intestinal obstruction (7%), vomiting (8%), nausea (9%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1-4) occurred in 71% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 67% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (69%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 1 and Table 2 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRATA.

<table>
<thead>
<tr>
<th>Table 1: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRATA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 1-4</strong></td>
</tr>
<tr>
<td><strong>N=663</strong></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
</tr>
<tr>
<td>Anemia*</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
</tr>
<tr>
<td>Neutropenia*</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td><strong>Infectious and Infestations</strong></td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
</tr>
<tr>
<td>AST/LAT elevation</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
</tr>
<tr>
<td>Acute kidney injury</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

*CDIAC®—Common Terminology Criteria for Adverse Events version 4.02

Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.

Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutrophil infection and neutrophil sepsis.

Based on animal studies, ZEJULA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (13.1) of full prescribing information).

8.5 Geriatric Use

In PRIMA, 98% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mild (Clcr 60 to 89 mL/min) to moderate (Clcr 30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (WHO-LDOW) criteria. The safety of ZEJULA in patients with moderate/severe hepatic impairment is unknown.

10 OVERDOSAGE

There is no specific treatment in the event of ZEJULA overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

17 PATIENT COUNSELING INFORMATION

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

MEDICATION

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematologic toxicity or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZEJULA (see Warnings and Precautions (5.2)).

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection (see Warnings and Precautions (5.2)).

Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first two months, then monthly for the first year of treatment, and then periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated (see Warnings and Precautions (5.6)).

Dosing Instructions

Inform patients on how to take ZEJULA (see Dosage and Administration (2.2) of full prescribing information). ZEJULA should be taken once daily. Advise patients that if they miss a dose of ZEJULA, not to take an extra dose to make up for the one that was missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole; ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy (see Warnings and Precautions (5.8)).

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after receiving the last dose (see Use in Specific Populations (8.3)).

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose (see Use in Specific Populations (8.2)).

Trademarks are owned by or licensed to the GSK group of companies, Manufactured for GlaxoSmithKline Research Triangle Park, NC 27709 ©2020 GSK group of companies.
Novel Tubulin-Targeting Therapies Make Headway
by DANIEL KEIFENHEIM, PhD

MICROTUBULES, WHICH ARE cytoskeletal proteins that are integral to cell functions, have represented an attractive target for anticancer drug development for more than 60 years. The first microtubule-targeting agents (MTAs) were introduced in the late 1950s, beginning with vinca alkaloids and followed several years later by taxanes.1,4 Since then, many MTAs have been developed for the treatment of numerous cancer types.

Now advances in understanding the role of the microtubule cytoskeleton in cancer cells have generated optimism that novel MTAs will provide increased efficacy with less toxicity. Clinical findings have recently been reported for 2 of the more advanced emerging tubulin-targeting agents, VERU-111 and plinabulin.5,6

THE ROLE OF MICROTUBULE FUNCTION Microtubules are polymers of tubulin heterodimers, each of which consists of an α- and β-tubulin monomer. These heterodimers bind in chains to form 13 protofilaments that bind laterally to create a hollow microtubule 24 nm in diameter.7

The dynamics between intracellular pools of tubulin heterodimers and microtubule polymers are highly regulated. Microtubule dynamics are determined by the guanine triphosphate (GTP) nucleotide bound to each tubulin heterodimer. When GTP is hydrolyzed to guanine diphosphate (GDP) during polymerization, the affinity of GDP-bound tubulin for adjacent tubulin molecules weakens, and this dynamic instability of microtubules results in periods of polymerization and depolymerization. During polymerization, GDP-bound tubulin is added to the growing "plus" end of the microtubule to form a stable GTP cap. During depolymerization, GDP-bound tubulin rapidly disassembles from the microtubule.8

In initial preclinical research, investigators noted that MTAs arrest the cell cycle by inhibiting mitotic spindle formation, leading to cell death.9 However, in human tumors, in which cell growth is slower when compared with that of cultured cells, mitotic disruption may not play as large a role in the activity of MTAs because fewer cells will be in mitosis at any given time. In addition to mitotic disruption, MTAs can have antiangiogenic and antimetastatic activity. However, the complex environment of a human tumor makes it difficult to determine the exact mechanism of MTA-induced cell death.8

MICROTUBULE-TARGETING AGENTS MTAs can be classified into 2 broad groups: those that stabilize microtubule formation and those that destabilize microtubule formation (FIGURE10) Microtubule-stabilizing agents (MSAs) include taxanes and epothilones whereas microtubule-destabilizing agents (MDAs) include vinca alkaloids and colchicines.10 Taxanes bind to the inner, luminal side of the microtubule, stabilizing it by strengthening the longitudinal tubulin binding affinity.10 Epothilones mimic the microtubule-stabilizing effect of the taxols, act as competitive inhibitors of taxol binding, and have similar microtubule affinity.11 By contrast, in the MDA group, vinca alkaloids cause depolymerization by forming tubulin paracrystals whereas colchicine blocks microtubule function by binding tubulin and blocking polymerization.10 Although all MTAs have distinct binding sites and actions, most of these compounds show notably similar effects on microtubules, especially at the lowest effective drug concentrations.10

FDA-APPROVED MTAs The FDA has approved at least 8 microtubule inhibitors for use in cancer.12,13 MSAs include paclitaxel and docetaxel, which are approved for use in a number of cancer types. Cabazitaxel (Jevtana), also an MSA, is indicated in combination with prednisone for patients with metastatic castration-resistant prostate cancer (mCRPC),14 and nab-paclitaxel (Abraxane) is approved for metastatic breast cancer, non–small cell lung cancer (NSCLC), and metastatic pancreatic adenocarcinoma.15 The epothilones eribulin mesylate (Halaven) and ixabepilone (Ixempra) are both approved for metastatic or advanced breast cancer;16,17

FIGURE. Diverse Binding Sites for Therapies Aimed at the Microtubule10

\[\text{Tubulin-GDP} \quad \text{Tubulin-GDP or GDP-Pi} \quad \text{Tubulin-GTP}\]

GDP, guanine diphosphate; GTP, guanine triphosphate.

eribulin also is indicated for unresectable or metastatic liposarcoma.

In the category of MDAs, the vinca alkaloid drug family is comprised of vinorelbine tartrate, used in combination with cisplatin and as monotherapy for metastatic NSCLC, and vindesine sulfate liposome injection (Marqibo), indicated for the treatment of relapsed acute lymphoblastic leukemia.13

As noted, colchicine is a microtubule-destabilizing agent; it induces GTP hydrolysis to convert GTP-bound tubulin to GDP-bound tubulin and promote disassembly. Although the FDA has approved colchicine for the treatment of gout and Mediterranean fever, therapeutic uses have been limited due to its toxicity.14 However, colchicine binding site inhibitors are less susceptible to efflux pumps, a main mechanism for acquired drug resistance. Additionally, colchicine derivatives inhibit angiogenesis, one of the hallmarks of cancer, by disrupting microtubule ability to regulate vasculature network formation.7

**COLCHICINE-TARGETING AGENTS**

Several compounds that target the colchicine binding site are currently in clinical development. These include OX14503 (combretastatin A1 diphosphate; CAI), for which the FDA has granted a rare pediatric disease designation for development as a treatment for acute myeloid leukemia (AML) due to genetic mutations that disproportionately affect pediatric patients. The agent is a prodrug of combretastatin A1, a chemical originally isolated from a species of willow tree bark, that targets the colchicine binding site to destabilize microtubules. In prior clinical findings, OX14503 in combination with standard cytarabine elicited 4 complete remissions among 26 evaluable adults with AML.7,19

Other agents in the colchicine class include lisavanbulin (BAL101553) and plinabulin.20,21 Investigators are evaluating lisavanbulin in a phase 1 trial (NCT03250299) in combination with standard radiotherapy for patients with newly diagnosed MGMT promoter unmethylated glioblastoma. Plinabulin (also called NPI-2358 or BPI-2358), which is administered intravenously, is being developed in the United States and China under breakthrough therapy designations for the prevention of chemotherapy-induced neutropenia.6

The agent is being evaluated in the phase 3 Protective 2 trial (NCT03294577) in combination with pegfilgrastim (Neulasta) in patients receiving docetaxel, doxorubicin, and cyclophosphamide and in the phase 3 Protective-1 study (NCT03102606) in patients with advanced solid tumors receiving myelosuppressive chemotherapy.

In topline findings from Protective 2, the combination of plinabulin plus pegfilgrastim met the primary end point by demonstrating a statistically significant improvement in the rate of prevention of grade 4 neutropenia versus pegfilgrastim alone in cycle 1 of therapy (31.5% vs 13.6%, respectively; P = .0015). Key secondary end points were also met, including duration of severe neutropenia from day 1 to day 8 in the first cycle, and mean absolute neutrophil count nadir during cycle 1 (P = .0002).6

**VERU-111**

The novel tubulin inhibitor VERU-111 is a first-in-class next-generation oral MTA, which targets both α and β tubulin, binding at the α-β tubulin interface and targeting the colchicine binding pocket.22-23 To date, VERU-111 has shown antitumor activity in several preclinical tumor models.24-27 The preclinical profile of VERU-111 suggests that this agent has high oral bioavailability and a favorable toxicity profile with no neurotoxicity, neutropenia, or myelosuppression.24 VERU-111 is also not a substrate for multidrug resistance proteins such as P-glycoprotein, MRPs, and BCRP, suggesting the agent may be better able to maintain its inhibition of microtubule activity.22,23

“[In preclinical studies, VERU-111 can bind to colchicine, resulting in inhibition of microtubule polymerization,” Mark C. Markowski, MD, PhD, an assistant professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, said during a presentation at the European Society for Medical Oncology (ESMO) Virtual Congress 2020. “It can also decrease the production of several β isoforms of tubulin. Unlike other taxane chemotherapies, it’s not a substrate for multidrug resistant proteins or CYP3A4.”25

Markowski and colleagues are evaluating VERU-111 in a phase 1b/2 clinical trial (NCT03752099) in patients with mCRPC whose disease progressed while receiving an alternative AR-blocking agent such as abiraterone acetate (Zytiga) or enzalutamide (Xtandi) in men with mCRPC whose disease has progressed while receiving an AR-targeting therapy. The primary end point is rPFS, with secondary end points including overall survival, pain progression, and PSA responses. Enrollment for the trial is estimated at 250 patients.23

VERU-111 has demonstrated antitumor activity in preclinical models of other cancer types, such as taxane-resistant cervical, lung, and ovarian cancers and other solid malignancies, as well as in human promyelocytic leukemia.23 Additionally, VERU-111 is being studied in a phase 2 trial (NCT04388826) as a treatment for severe acute respiratory syndrome coronavirus 2, which causes coronavirus disease 2019. The trial is seeking to enroll 40 patients.
IN HER2+ EARLY BREAST CANCER (EBC), UNDERSTAND HER RISK OF RECURRENCE

HER2=human epidermal growth factor receptor 2.
HER RISK OF RECURRENCE REMAINS, EVEN AFTER NEOADJUVANT TREATMENT

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.¹,²

The CTNeoBC pooled-analysis assessed the risk of recurrence following neoadjuvant treatment among patients with breast cancer, including HER2+ EBC, based on historic data.¹

The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.¹

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.¹
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease. 1

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes. 1

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery. 1,2

**Association between pCR and event-free survival (EFS)** in the HER2+ subgroup analysis of the CTNeoBC study1

*EFS was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.1

1,989 patients with HER2+ tumors were included in the subgroup analysis. 55% of which did not receive a full year of adjuvant HER2-targeted monotherapy treatment.1

**While there are different paths you can choose for your patient with HER2+ EBC, her treatment shouldn’t stop at neoadjuvant therapy.**
Discover possible adjuvant treatment options that may be right for her*:

For patients who achieve pCR, visit PCRinEBC.com

For patients who do not achieve pCR, visit NoPCrinEBC.com

*There may be other treatment options available for your patients.

Evolving Data for CLL Set Stage for Frontline Therapy

**by CHRISTINA T. LOGUIDICE**

**IN THE PAST 3 YEARS**, novel agents have shaken up the treatment landscape for patients with chronic lymphocytic leukemia (CLL). Deciding between agents in the first-line setting has become increasingly complex, as data for pathway inhibitors, specifically Bruton tyrosine kinase inhibitors (BTKis) and BCL-2 inhibitors, show promising therapeutic response. While individual patient risk factors such as comorbidities and age at diagnosis remain a key stratification factor, cytogenetic abnormalities including 17p deletions (del[17p]) and TP53 and IGHV mutations are reliable prognostic tools to identify patients with CLL who may be at a higher risk of early progression.

“Selection and choice of first-line therapy is an important decision to make for patients with CLL,” moderator William G. Wierda, MD, PhD, said. “We have options, and we have a lot of data to support our decisions. We also have prognostic factors to help us prioritize and select frontline therapy.” In a recent OncLive Peer Exchange®, a panel of hematologic experts discussed the paradigm shift in frontline therapy options for patients with CLL. The panelists focused on the latest data for novel BTKis and discussed progress in overcoming acquired resistance to BCL-2 inhibitors.

**ADVANCES IN BTKis**

“There has been a very rapid shift in therapies for CLL. There have been many new approvals,” Nicole Lamanna, MD, said. She noted that FDA-approved BTKis now include ibrutinib (Imbruvica) and acalabrutinib (Calquence), which can be used as monotherapy or in combination with a CD20 monoclonal antibody in the first- and subsequent-line settings, and that she expects zanubrutinib (Brukinsa) to be approved as well.

The recently published follow-up results from arm C of the SEQUOIA trial (NCT03336333), in which treatment-naïve patients with the high-risk cytogenetic marker del(17p) received zanubrutinib, showed an overall response rate of 94.5% at a median follow-up of 18.2 months, with 3.7% achieving a complete response or complete response with incomplete bone marrow recovery, 87.2% a partial response (PR), 3.7% a PR with lymphocytosis, 4.6% stable disease, and 0.9% progressive disease. The estimated 18-month progression-free survival (PFS) rate was 88.6%, and the estimated overall survival rate was 95.1%. Treatment was generally well tolerated, with only 4 patients (3.7%) discontinuing treatment because of an adverse effect (AE). The most common AEs, occurring in at least 10% of treated patients, included contusion, upper respiratory tract infection, decreased neutropenia/neutrophil count, gastrointestinal effects including diarrhea, nausea, constipation, rash, back pain, cough, arthralgia, and fatigue.

“We all would agree that for patients with a 17p or a TP53 abnormality, these are patients who should receive a novel agent. Our longest data happen to be with BTK inhibitors in this subgroup, but certainly there are data for venetoclax-based combinations as well in this poor prognostic group of patients. That’s an important factor to know about prior to treating your patient,” Lamanna said.
She also emphasized that patients’ chromosomal abnormalities may change following various treatments, making it important to assess patients’ cytogenetic markers before starting any subsequent treatments.

**NEW AND EMERGING VENETOCLAX COMBINATIONS**

Considerable progress has also been made with venetoclax, the first selective, orally bioavailable BCL-2 inhibitor. It has shown good therapeutic responses as a monotherapy in patients with CLL irrespective of the presence of adverse clinical or genetic features, including in patients with relapsed or refractory CLL. A challenge, however, has been that most patients ultimately become resistant to this treatment, which has led to the investigation of a variety of venetoclax combination approaches.

“Recently, we had the [approval of] the BCL-2 inhibitor venetoclax in combination with obinutuzumab,” Lamanna said (TABLE). Approval was based on data from CLL14 (NCT02242942), a randomized, multicenter, open label, actively controlled trial, which randomly assigned 432 patients with previously untreated CLL with coexisting medical conditions 1:1 to venetoclax (Venclexta) plus obinutuzumab (Gazyva) (VenG; n = 216) or obinutuzumab plus chlorambucil (GCib; n = 216). The primary end point was investigator-assessed PFS. Data from an updated analysis presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program showed that after a median follow-up of 39.6 months, the median PFS was not reached in the VenG arm versus 35.6 months in the GCib arm (HR, 0.31; 95% CI, 0.22-0.44; P < .001). The estimated 3-year PFS rate was significantly higher in the VenG arm than in the GCib arm at 81.9% versus 49.5%, respectively. Benefit was observed regardless of high-risk cytogenetic features, including TP53 deletion/mutation or the presence of unmutated immunoglobulin heavy-chain variable region genes.

“The CLL14 study, in my opinion, is one of the most important studies for CLL,” Mazyar Shadman, MD, MPH, said. “Basically, it introduced time limits and chemotherapy-free treatment in the first-line setting. The benefit was seen in all the known risk groups for CLL, including those with TP53 abnormality or unmutated IGHV gene. So here, because we are talking about the fixed-duration therapy, the depth of response becomes very important and one of the secondary end points of this study was the rate of MRD [minimal residual disease] eliminations.” Three months after treatment completion, a higher rate of undetectable MRD (10⁻⁴) was observed in the VenG arm (75.5%) versus in the GCib arm (35.2%; P < .001). Further, at 18 months after treatment, 47.2% of patients in the VenG arm had undetectable MRD compared with 7.4% in the GCib arm.

“This data is very impressive because we know from venetoclax-based therapies that the duration of response and progression-free survival are directly correlated with the depth of response, meaning that if you receive that undetectable MRD, the PFS would be longer,” Shadman said.

Additionally, venetoclax is showing promise combined with BTKis. “I should give credit to the University of Texas MD Anderson Cancer Center for publishing data that show for the first time the preclinical synergy between BTK inhibitors and BCL-2 inhibitors. We are seeing this now translate to clinical efficacy as well, not just additive properties between these drugs. We can utilize the modulation of different pathways and then hit them hard with both drugs,” John N. Allan, MD, said.

In a phase 2 study (NCT02756897) that assessed ibrutinib plus venetoclax in 80 previously untreated high-risk older patients with CLL who had del(17p), mutated TP53, 11q deletion, or unmutated IGHV, 88% had complete remission or complete remission with incomplete count recovery and 61% had remission with undetectable MRD after 12 cycles of combined treatment. Responses were observed across all risk groups. No new safety concerns were observed. Three patients had laboratory evidence of tumor lysis syndrome, but none developed clinical evidence of this complication or had to cease treatment because of it.

The panelists were particularly excited about upcoming updates from the phase 2 CAPTIVATE trial (NCT02910583), which they noted has 2 particularly well-designed cohorts that will enable cross-study comparisons to help answer some key questions in CLL. “We will find out if a patient population seems to benefit from maintenance. We’re going to start to learn what to do with MRD,” said Allan, who is an investigator on the trial. “The 25% of patients who don’t achieve MRD...
are randomized to monotherapy ibrutinib versus continuing the doublet of venetoclax and ibrutinib followed by a period of continual ibrutinib. That will be an interesting group to see who is not reaching MRD and then how well they do.” Allan explained this will help investigators determine if there is potential for MRD to deepen in those patients over time. “Right now, a lot of the data show that patients either reach MRD negativity or don’t within the first year or two. After the second year, MRD doesn’t seem to deepen. There is something about the biology of CLL that keeps MRD from deepening,” he said.

After this Peer Exchange, data from CAPTIVATE supported the fixed-duration treatment regimen of ibrutinib plus venetoclax in patients who had confirmed undetectable MRD, defined as undetectable in both peripheral blood and bone marrow serially over at least 3 cycles. Patients 70 years or younger received 3 cycles of lead-in ibrutinib followed by 12 cycles of ibrutinib plus venetoclax. The primary end point of disease-free survival (DFS) in these patients was defined as survival without progression or MRD relapse.

Of 149 randomized patients, 86 (58%) had confirmed undetectable MRD and were randomized to placebo (n = 43) or maintenance ibrutinib (n = 43). The 1-year DFS rate was not significantly different for patients who received placebo (95.3%; 95% CI, 82.7%-100%) versus those who received ibrutinib (100%; 95% CI, 100%-100%; P = .1475) and ibrutinib plus obinutuzumab with an ibrutinib, obinutuzumab, and venetoclax triplet in previously untreated older adults (≥ 70 years) with CLL in need of therapy. The trial is still enrolling patients through the National Cancer Institute’s National Clinical Trials Network. Similarly, EA9161 is a randomized phase 3 trial comparing the same combination in younger patients (≤ 69 years).

“We are limited in terms of understanding the benefit of that anti-CD20, whether it is going to help or not. We’ll start to see MRD rates, and these are all very similar patient populations, so we will be able to make comparisons across studies to see if these MRD rates are any different or can have an additive effect,” Allan said, noting that these trials will help answer the question of whether patients can achieve an 80% bone marrow disease-negative state with the addition of an anti-CD20 to a BTKi and BCL-2 doublet.

**SELECTING OPTIMAL FIRST-LINE THERAPY**

The panelists agreed that choosing between BTKi and BCL-2 inhibitor therapy in the first line are highly individualized decisions.

“The choice in my mind is probably going to be a BTK inhibitor versus venetoclax/obinutuzumab,” John M. Burke, MD, said. “The choice for me doesn’t have as much to do with the disease, the biology, the gene mutation, etc. A lot of it comes down to 2 other factors related to the patient and the patient’s preferences. For example, venetoclax/obinutuzumab is a 1-year fixed duration therapy. That’s a big difference from indefinite therapy with a BTK inhibitor,” he said.

The other factor is a patient’s comorbidities, such as the presence of underlying cardiac issues, atrial fibrillation, or use of an anticoagulation therapy, which will play a role in therapeutic selection based on the toxicity profiles of the agents, Burke added.

“For the patient who doesn’t have an obvious contraindication, it comes down to patient preference.”

One notable exception is in patients who receive a diagnosis under aged 65 years, are deemed fit, or have an IGHV mutation and no del(17p) or TP53 aberrancy according to fluorescence in situ hybridization results.

“That is a group of patients that seems to have a particularly good outcome with FCR [fludarabine, cyclophosphamide and rituximab (Rituxan)] and chemotherapy,” Burke said. “A significant percentage of this subset of patients treated with FCR continue to be disease free well beyond 10 years now. So I think the FCR regimen or something similar to that still comes into play as an option for those patients.”

**REFERENCES**

BETTER IS HOME TO NEW JERSEY’S BEST CANCER CENTER

U.S. News & World Report has recognized Hackensack Meridian John Theurer Cancer Center at Hackensack University Medical Center as the best cancer center in all of New Jersey. And as a member of one of just 16 NCI-designated cancer consortia, we have distinguished ourselves as New Jersey’s premier cancer center—offering nationally recognized cancer specialists, clinical trials and immunotherapy including CAR T-Cell.

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.