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ROGERIO C. LILENBAUM, MD

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BLENREP
belantamab mafodotin-blmf
for injection 100 mg

NOW APPROVED

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

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BRIEF SUMMARY

BLENREP
(belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

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 (5.2)].

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 (see Clinical Studies 1(4) of full Prescribing Information). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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>Grade 1</td>
<td>Continue treatment at current dose.</td>
</tr>
<tr>
<td>Corneal examination finding(s): Mild superficial keratopathy* Change in BCVA: Decline from baseline of 1 line on Snellen Visual Acuity</td>
<td></td>
</tr>
<tr>
<td>Grade 2</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>Corneal examination finding(s): Moderate superficial keratopathy* 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>
</tbody>
</table>

* 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.

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 (68°F to 77°F [20°C to 25°C]).
- 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 36°F to 46°F (2°C to 8°C) or at room temperature (68°F to 77°F [20°C to 25°C]) 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 vials.
• 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 polysulfone (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.

4 CONTRAINDICATIONS
None.

5 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 infectious 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 in 20/200 or worse in the better-seeing eye in 1.4%. 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 opthalmic 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 cell counts 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 [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 dose 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%). Permanently discontinued 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. 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 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyltransferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (23%) and thrombocytopenia (5%). 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 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyltransferase 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 Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Keratopathy(1)</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuity(1)</td>
<td>53</td>
</tr>
<tr>
<td>Blurred vision(1)</td>
<td>22</td>
</tr>
<tr>
<td>Dry eyes(2)</td>
<td>14</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue(2)</td>
<td>20</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions(1)</td>
<td>21</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection(1)</td>
<td>11</td>
</tr>
</tbody>
</table>

\(1\) Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

\(2\) Visual acuity changes were determined upon eye examination.

\(3\) Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

\(4\) Dry eyes included dry eye, ocular discomfort, and eye pruritus.

\(5\) Fatigue included fatigue and asthenia.

\(6\) Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

\(7\) Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

- **Eye Disorders**: Photophobia, eye irritation, infective keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders**: Vomiting, Diarrhea.
- **Infections**: Pneumonia.

Investigations: Albuminuria. Table 4 summaries the laboratory abnormalities in DREAMM-2.

### Table 4. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
<td>2</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, 2/274 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 of therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, 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-blmf has 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 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-blmf. 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
Female: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Male: Because of the potential for gonotoxicity, 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 or 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)].
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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 58.
Expert Sees Need for Better Guideline Adherence in NSCLC

by LARRY HANOVER

Lung cancer specialist Rogerio C. Lilenbaum, MD, who serves as director of the Banner MD Anderson Cancer Center in Arizona, will bring his blend of real-world patient-centered oncology to the 18th Annual Winter Lung Conference®, which will be held virtually on February 5-7, 2021. One of the discussions at the conference will involve the need to follow treatment guidelines for mutational testing for patients with advanced non–small cell lung cancer (NSCLC).

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Biomarker Testing Needs Broader Uptake

THE CLINICAL UTILITY OF molecular tumor analysis in patients with advanced non–small cell lung cancer (NSCLC) has grown considerably since the mid-2000s, when investigators established an association between activating EGFR mutations and response to EGFR-targeting therapies.¹ Today, the National Comprehensive Cancer Network recommends testing for 7 different alterations,² and several additional targets are likely to be added as a result of ongoing clinical studies.

Nevertheless, although guideline panels in oncology societies throughout the world agree on the importance of biomarker testing for patients with lung cancer, the implementation of this strategy varies in clinical practice, not only in the United States but also in other developed nations, according to lung cancer experts.³

Testing rates for EGFR mutations and ALK translocations have reached as high as 87% and 69%, respectively, in 2018 analyses—a dramatic improvement since those biomarkers were integrated into guideline recommendations over the past decade but less than universal adoption. There’s a paucity of information about testing for other aberrations, such as ROS1 and BRAF abnormalities, but one study found that only 28% of eligible patients were tested for ROS1 alterations. “Clearly, there is considerable room for improvement,” Nathan A. Pennell, MD, PhD, and colleagues wrote in their analysis.³

That is a sentiment with which Rogerio C. Lilenbaum, MD, would agree. Guideline adherence in biomarker testing and early-stage immunotherapy is among the clinical priorities that Lilenbaum discusses in the cover story of this issue of OncologyLive⁴. As director of Banner MD Anderson Cancer Center in Gilbert, Arizona, Lilenbaum supports integrating guideline recommendations into clinical pathways embedded into electronic medical records. “I believe in the power of guidelines,” he says.

Lilenbaum and colleagues will discuss biomarker testing during the opening session of the 18th Annual Winter Lung Cancer Conference⁵, which he is cochairing. The conference, hosted by Physicians’ Education Resource (PER), LLC, will be held February 5 to 7, 2021, as a virtual meeting. Another session will feature a roundtable discussion about which set of guidelines conference attendees find useful for guiding their practice. Other sessions will offer expert insights into many other real-word treatment questions.

Although conversations about guidelines may not seem as compelling as presentations on exciting new data, the importance of incorporating best practices into clinical routines cannot be overstated. Identifying the barriers that practicing oncologists face in implementing such recommendations is an important part of the conversation.

We invite you to join that conversation by attending the conference. For more information, visit https://bit.ly/37oLomu.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
Indication

GAVRETO is a kinase inhibitor indicated for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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

Important Safety Information

Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4 and 0.6% with fatal reactions. Monitor for pulmonary symptoms indicative of interstitial lung disease (ILD)/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. 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 GAVRETO based on severity of confirmed hypertension.

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased AST occurred in 69% of patients, including Grade 3/4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 17 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥3 hemorrhagic events occurred in 2.57% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 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 GAVRETO after resolution of wound healing complications has not been established.

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. Common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected) and increased alanine aminotransferase (ALT).

Avoid coadministration with strong CYP3A inhibitors. Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration cannot be avoided, increase the GAVRETO dose.

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

Please see Brief Summary of full Prescribing Information on adjacent pages.
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
This brief summary does not include all the information needed to use GAVRETO safely and effectively. See full Prescribing Information for GAVRETO.

GAVRETO™ (pralsetinib) capsules, for oral use. Initial U.S. approval: 2020

INDICATIONS AND USAGE
GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension
Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. 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 GAVRETO based on the severity.

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years).

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

Hemorrhagic Events
Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

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

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, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 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 GAVRETO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

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

• Interstitial Lung Disease/Pneumonitis
• Hypertension
• Hepatotoxicity
• Hemorrhagic Events
• Risk of Impaired Wound Healing

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 pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET altered solid tumors in ARROW. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

RET Fusion-Positive Non-Small Cell Lung Cancer
The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW. The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients; fatal adverse reaction which occurred in > 1 patient included pneumonia (n = 3) and sepsis (n = 2).
Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

The most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected), and increased alanine aminotransferase (ALT).

Table 4 summarizes the adverse reactions in ARROW.

Table 4: Adverse Reactions (≥15%) in Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue¹</td>
<td>35</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
</tr>
<tr>
<td>Edema²</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea³</td>
<td>24</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>16</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain⁴</td>
<td>32</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension⁵</td>
<td>28</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
</tr>
<tr>
<td>Cough⁶</td>
<td>23</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Pneumonia⁷</td>
<td>17</td>
</tr>
</tbody>
</table>

¹ Fatigue includes fatigue, asthenia
² Edema includes edema peripheral, face edema, periorbital edema, eyelid edema, edema generalized, swelling
³ Diarrhea includes diarrhea, colitis, enteritis
⁴ Musculoskeletal pain includes back pain, myalgia, arthralgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal stiffness, arthritis, spinal pain
⁵ Hypertension includes hypertension, blood pressure increased
⁶ Cough includes cough, productive cough, upper-airway cough syndrome
⁷ Pneumonia includes pneumonia, atypical pneumonia, lung infection, pneumocystis jiroveci pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal
*Only includes a Grade 3 adverse reaction

Table 5: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</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>69</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>42</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>40</td>
</tr>
<tr>
<td>Increased calcium (corrected)</td>
<td>29</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>27</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>54</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>52</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</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 83 to 94 patients.

Clinically relevant laboratory abnormalities < 20% of patients who received GAVRETO included hyperphosphatemia (10%).

**DRUG INTERACTIONS**

**Effects of Other Drugs on GAVRETO**

**Strong CYP3A Inhibitors**

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose.

**Strong CYP3A Inducers**

Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration cannot be avoided, increase the GAVRETO dose.
USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily (see Data). 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 2-4% and 15-20%, respectively.

Data

Animal Data
In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.5-2.2 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.5 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

Lactation

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

Females and Males of Reproductive Potential

Based on animal data, GAVRETO can cause embryolethality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily.

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

Contraception
GAVRETO can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal contraceptives ineffective.

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

Infertility
Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility.

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

Animal Toxicity Data
In a 4-week repeat-dose toxicity study in non-human primates, physeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physeal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicity study, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Geriatric Use
Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

Hepatic Impairment
GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST).

Manufactured for: Blueprint Medicines Corporation, Cambridge, MA 02139, USA

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For more information, go to www.GAVRETO.com or call 1-888-258-7768.
COVID-19 Takes Science on a Roller-Coaster Ride

by MAURIE MARKMAN, MD

FINALLY, WE HAVE SOME GOOD NEWS about coronavirus disease 2019 (COVID-19), and it is very good news. Early reports suggest that at least 2 COVID-19 vaccines are both highly active, preventing approximately 95% of viral-associated illness including serious events, and are safe at least over the short term, measured by several months following vaccination. It is anticipated that vaccination of at-risk medical personnel and other first responders, as well as the most vulnerable populations, will begin before the end of the year or early in 2021, followed by widespread availability to the general public of several potentially very active and safe vaccines.1,2

Of course, this development and the impressive favorable early efficacy and toxicity results, are welcome. However, it is important to acknowledge there is nothing in the mandated process of rigorous, nonbiased, methodical, and careful external monitoring and review associated with the evaluation of these and other vaccine candidates that could have ensured these most favorable outcomes.

The scientific process itself, whether undertaken in the laboratory, the clinic, or in the even more complex sphere of public health, may be painfully slow to reveal data that can form the basis for meaningful and valid conclusions. In addition, initial and subsequent scientifically rational and encouraging hypotheses may lead to quite discouraging results when examined in the real world of human health and disease.

In a pandemic, the public and its leaders yearn for relatively simple answers that can lead to solutions and forceful actions such as preventing serious infection and hospitalizations, treating active illness, and developing safe and effective vaccines quickly made available to the public. Responses from the scientific community that are frequently and appropriately nuanced may not be well received. Further, the concept of changing recommendations, perhaps even resulting in contradictory suggestions based on evolving data, is difficult for many to understand and accept, particularly when such advice may have major economic and societal implications such as shutting businesses and closing schools.3,4

One can find no better examples than the issue of wearing masks in public or the need for social distancing to appreciate the confusion felt by the public.5 What is the evidence to support the public health value of these strategies and why have specific recommendation changed over the course of the pandemic?

It may not be terribly difficult for someone versed in the scientific method to appreciate the time required to obtain reliable data and the relevance of the various levels of evidence such as randomized trials, nonrandomized prospective observational studies, retrospective reviews of the electronic medical record, individual case reports, or population-based modeling efforts. However, most individuals and families faced with economic and personal hardships resulting from this pandemic will not feel comfort in these process issues.

So when the president of the United States rather forcefully declares that a well-established pharmaceutical agent (ie, hydroxychloroquine) offers major benefit in preventing serious complications of a COVID-19 infection and the clinical scientific community responds that this drug requires time-consuming detailed study in properly designed evidence-based randomized trials before it should be widely employed, it is not difficult to understand which voice may have the greater influence for many members of our society.3

Finally, it is relevant to acknowledge the unfortunate but measurable divide in this country for trust in science based on political affiliations.6 This is a most distressing situation because the basic goal of scientific research and clinical investigation is to improve our understanding of biology and human illness and to develop strategies to enhance the lives of all members of society. Individuals in the public health community devote their professional careers to applying the best available population science to help achieve these goals.

Something is terribly wrong if this simple yet profound idea has not been effectively communicated to the public. In the absence of such understanding and trust, is it any wonder than many refuse to listen to the extensive and highly relevant experience of members of the scientific and public health communities during a pandemic?

Of course, the severity of COVID-19 requires innovation in the exploration of the clinical utility and safety of novel strategies to treat and prevent this viral infection. The recent announcements regarding vaccine development are testimony to the successful efforts of many in the scientific, pharmaceutical, and governmental health communities.

One can hope that strategies designed to rapidly but rigorously explore new therapeutics can similarly be applied in the future to novel approaches in cancer management, including the exploration of the hundreds of molecularly based antineoplastic agents in pharmaceutical/biotech company pipelines that have the potential to meaningfully affect the quality and length of life for patients with malignant disease.

In the absence of such bold efforts to effectively examine the utility of these agents in as short a time as possible, how many lives of patients with cancer will be needlessly shortened? ■

REFERENCES

FDA DIGEST

**Naxitamab-gqgk Enters the Paradigm for R/R High-Risk Neuroblastoma**

The FDA has granted an accelerated approval to naxitamab-gqgk (Danyelza) in combination with granulocyte-macrophage colony-stimulating factor as a treatment for pediatric patients 1 year and older with relapsed/refractory (R/R) high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, a minor response, or stable disease to prior treatment.

Naxitamab is a monoclonal antibody directed at GD2, which is highly expressed in various neuroectoderm-derived tumors and sarcomas. The decision is supported by clinical evidence from 2 studies in patients with high-risk neuroblastoma with R/R disease.

Results from 38 patients included in the efficacy analysis of Study 12-230 (NCT01757626) showed an overall response rate of 34% (95% CI, 20%-51%). The complete response rate was 26%, and the partial response rate was 8%. Of the responders, 23% had a response lasting longer than 6 months.

Findings from Study 201 (NCT03363373) showed that treatment with the agent in 22 patients included in the efficacy analysis led to an overall response rate of 45% (95% CI, 24%-68%) and a complete response rate of 36%. According to the agent’s developer, Y-mAbs Therapeutics, Inc, the approval is contingent on results demonstrating continued clinical benefit from Study 201.

A black box warning regarding adverse events for naxitamab lists serious infusion-related reactions and neurotoxicity, including severe neuropathic pain, transverse myelitis, and reversible posterior leukoencephalopathy syndrome.


**Sonalleve MR-HIFU System Gets Cleared for Use in Osteoid Osteoma**

The FDA has approved the Sonalleve MR-guided high-intensity focused ultrasound (MR-HIFU) system to treat patients with osteoid osteoma in the extremities. The treatment, which is manufactured by Profound Medical Inc, is designed to provide precise and controlled delivery of focused ultrasound energy into a lesion with the use of an external applicator.

The approval was based on data from 9 pediatric patients with osteoid osteoma in a single-group assignment study (NCT02349971) who were treated with external applicator.

Results showed a statistically significant decrease in pain scores within 4 weeks of treatment, with no pain medication used in 8 of the 9 patients after 4 weeks. Further, the device showed efficacy without technical difficulties and did not lead to serious adverse events.

Standard treatment options for patients with osteoid osteoma include surgical excision and CT-guided radiofrequency ablation. The latter is a more invasive method and requires drilling from the skin through muscle and soft tissue into bone, exposing the patient and operator to ionizing radiation.


**Loncastuximab Tesirine Moves Toward Approval for R/R DLBCL**

The antibody-drug conjugate loncastuximab tesirine (Lonca), designed to target and kill CD19-expressing malignant B cells, was granted a priority review from the FDA. The agent is being evaluated as a treatment for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). The FDA is scheduled to make a decision by May 21, 2021.

The biologics license application is based on data from the pivotal phase 2 LOTIS 2 trial (NCT03589469), a single-arm study of 145 patients with R/R DLBCL who have received 2 or more prior lines of therapy. Loncastuximab tesirine induced an overall response rate of 48.3% and a complete response rate of 24.1% in participants who had received at least 2 previous lines of systemic treatment. The median duration of response was 10.25 months.

Investigators are evaluating loncastuximab tesirine in a confirmatory phase 3 trial, LOTIS 5 (NCT04384484), in R/R DLBCL. Approximately 350 patients will be enrolled and treated with either with loncastuximab tesirine plus rituximab or standard immunochemotherapy.


**Pralsetinib Is Granted Approval for RET+ Thyroid Cancer**

The FDA has approved pralsetinib (Gavreto) for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy or RET fusion–positive thyroid cancer who require systemic therapy and who are refractory to radioactive iodine.

Findings from the multicenter, open label, multicohort phase 1/2 ARROW trial (NCT03037385) showed that among 55 patients with advanced or metastatic RET-mutant MTC who had received prior cabozantinib (Cabometryx) or vandetanib (Caprelsa), pralsetinib elicited an overall response rate (ORR) of 60% (95% CI, 46%-73%). Additionally, 79% of responders experienced responses that persisted for 6 months or longer.

Among 9 patients with RET fusion–positive thyroid cancer who were also refractory to radioactive iodine, the ORR reported with pralsetinib was 89% (95% CI, 52%-100%). All responders experienced responses that lasted for 6 months or longer.


**COVID-19 Delays Review of Liso-cel for R/R Large B-Cell Lymphoma**

The FDA has deferred action on the biologics license application for lisocabatagene maraleucel (liso-cel), according to the agent’s developer, Bristol Myers Squibb. Because of coronavirus disease 2019 (COVID-19)–related travel restrictions, an inspection of a third-party manufacturing facility in Texas was not completed. The agency was originally set to make a decision on the application by November 16, 2020. The FDA did not provide a new action date.

The CD19-directed chimeric antigen receptor T-cell therapy is under review for the treatment of adults with relapsed/refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. The application is based on data from the phase 1 TRANSCEND-NHL-001 (NCT02631044) study in which treatment with liso-cel resulted in an objective response rate of 73% (N = 256). In the 187 patients who responded, 53% achieved a complete response, with the time to first complete response or partial response occurring at a median of 1 month.

The median duration of response had not been reached at a median follow-up of 12 months. Patients remaining in response at 6 and 12 months were 60.4% and 54.7%, respectively.

Prior to the COVID-19 delay, the FDA extended the review period by 3 months for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy and who are refractory to radioactive iodine.

Among 9 patients with RET fusion–positive thyroid cancer who were also refractory to radioactive iodine, the ORR reported with pralsetinib was 89% (95% CI, 52%-100%). All responders experienced responses that lasted for 6 months or longer.

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
BREXUCABTAGENE AUTOLEUCEL (KTE-X19; TECARTUS) induced durable response in patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL), according to findings from the phase 2 ZUMA-2 trial (NCT02601313), leading to an FDA approval for use in this patient population on July 24, 2020.

The therapy is a CD19-directed genetically modified autologous T-cell immuno-therapy that binds to CD19-expressing cancer cells and normal B cells. Investigators enrolled 74 patients into the ZUMA-2 trial to explore the safety and efficacy of brexucabtagene autoleucel. All enrolled patients underwent leukapheresis, and 68 received the study drug. Overall, 87% of patients had an objective response, including complete responses in 62% of patients.

Javier L. Munoz, MD, MS, director of the lymphoma program at Mayo Clinic in Phoenix, Arizona, and a coauthor on the ZUMA-2 trial, said patients with R/R MCL face “an ominous prognosis,” but one that can hopefully be averted by the use of cellular therapies. In an interview with OncologyLive®, he discussed the efficacy of brexucabtagene autoleucel compared with existing treatments, safety concerns with chimeric antigen receptor (CAR) T-cell agents, and future investigations into this therapy.

Q What was noteworthy about the patient response data from ZUMA-2, particularly across patient subgroups?

High-risk features heralding poor prognosis and refractoriness to standard chemotherapy [for patients with R/R MCL] include high Ki-67, TP53 aberrations, and blastoid/pleomorphic variants. Interestingly, patients with high-risk features such as a TP53 mutation did seem to respond to brexucabtagene autoleucel, which could potentially open a pathway to help this group of patients, fulfilling a historically unmet need.

Q What is the mechanism of action for this therapy?

CAR T-cell therapies typically use a viral vector to genetically modify the T cells, reeducating them to seek and destroy a particular antigen present on tumor cells. Tisagenlecleucel [Kymriah] and axicabtagene ciloleucel [Yescarta] are approved by the FDA for patients with R/R aggressive B-cell lymphoma who express CD19, which is present in multiple B-cell malignancies. Lisocabtagene maraleucel is under evaluation in the same setting.

Brexucabtagene autoleucel is also an anti-CD19 CAR T-cell agent. That said, brexucabtagene autoleucel is peculiar in that there is an extra step in the manufacturing process to remove circulating CD19-expressing malignant cells in order to decrease the chances of exhaustion of anti-CD19 CAR T cells. T cells are collected from the patient, modified genetically in the laboratory, then reinjected in the patient. There these reinvigorated CAR T cells develop expansion—they have been called a “living drug”—then target malignant cells expressing CD19 for destruction.

Q What is important to know about cytokine release syndrome and neurological toxicity, both of which are included in the black box warning?

These novel cellular technologies are not for the faint of heart, as severe toxicities including death have been reported. Similar to the CAR T cells currently available for R/R aggressive B-cell lymphomas, serious adverse effects were reported in ZUMA-2. These included grade 3 or higher cytokine release syndrome in 15% of patients and grade 3 or higher neurologic events in 31%.

It takes a village to prescribe these cellular therapies safely, and we are grateful to count on an outstanding multidisciplinary team, which includes neurology, cardiology, infectious diseases, and intensive care that support us as needed through this journey. There were only 2 grade 5 infections in ZUMA-2, which is a testament that only a small minority of patients face lethal toxicities.

Q How does this therapy fit into the R/R MCL treatment paradigm?

The ZUMA-2 trial inclusion criteria required patients to have prior BTKi—[Bruton tyrosine kinase inhibitor] exposure to be eligible. Patients could have received 2 to 5 previous therapies. We know that the outcomes are very dismal for patients with MCL who relapse or who are refractory to treatment with BTKi—overall survival is measured in months. Brexucabtagene autoleucel is indicated for adult patients with R/R MCL. This incongruence between the inclusion/exclusion criteria and the label means that there is potentially a discrepancy in second line when it comes to previous exposure to BTKi.

It goes without saying that we will certainly follow the FDA-approved label for brexucabtagene autoleucel and will consider it for any adult patient with R/R MCL, including patients with high-risk features. That said, not every patient with R/R MCL may be able to receive CAR T cells due to performance status, comorbidities, or lack of social support or a caregiver. One size does not fit all, particularly in such a heterogeneous disease as MCL.

Q What are the next steps for brexucabtagene autoleucel?

We need to embrace clinical trials that allow prior CAR T-cell failure. Next steps for autologous CAR T cells include decreasing manufacturing time, improving the safety profile, addressing the feasibility of outpatient administration, and testing CAR T cells in earlier lines of therapy. For example, tisagenlecleucel and axicabtagene ciloleucel are currently available for patients with aggressive lymphomas in the R/R setting; nevertheless, investigators are studying CAR T cells in the second line and frontline. It would not be unexpected to see brexucabtagene autoleucel assessed in earlier lines of therapy for MCL.

The TRANSCEND-NHL-001 trial [NCT02631044] evaluated lisocabtagene maraleucel in several subtypes of lymphomas, including patients with R/R MCL, and I am excited to see data regarding CAR T cells in MCL. Additionally, allogeneic CAR T cells are under evaluation in clinical trials that will, hopefully, provide off-the-shelf cellular therapies that will bypass any delays seen during manufacturing. Finally, there are multiple trials addressing autologous and allogenic cellular therapies in R/R MCL, and we await those results with enthusiasm.

Disclosures: Dr Munoz reports relationships with Kite/Gilead and Juno/Celgene/Bristol Myers Squibb.
PIVOTAL CLINICAL TRIAL
ZUMA-2 (NCT02601313), a single-arm trial, enrolled 74 adults with R/R MCL previously treated with an anthracycline- or bendamustine-containing chemotherapy; an anti-CD20 antibody; and either of 2 Bruton tyrosine kinase inhibitors, ibrutinib (Imbruvica) or acalabrutinib (Calquence).

Commonly Reported Adverse Effects in ZUMA-2 Trial
The most common adverse effects (incidence ≥ 20%) were pyrexia, cytokine release syndrome, hypotension, encephalopathy, fatigue, tachycardia, arrhythmia, infection (pathogen unspecified), chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspnea, rash, insomnia, pleural effusion, and aphasia.

BASELINE PATIENT CHARACTERISTICS:
Efficacy Population (N = 60)

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
<th>65 (38 to 79)</th>
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<tbody>
<tr>
<td>83% of patients had stage IV disease</td>
<td></td>
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<tr>
<td>23% of patients had blastoid MCL</td>
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<tr>
<td>Patients received a median number of 3 prior therapies</td>
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Baseline bone marrow examinations
33% of patients had baseline examinations

Prior therapies (%)
- 35%
- 43%
- 60%

FDA approval—July 24, 2020
FDA grants accelerated approval to brexucabtagene autoleucel (Tecartus) for adults with relapsed or refractory mantle cell lymphoma (R/R MCL).

Mechanism of action:
- Brexucabtagene autoleucel is a CD19-directed genetically modified autologous T-cell immunotherapy that binds to CD19-expressing cancer cells and normal B cells.

How supplied:
- An infusion bag containing approximately 68 mL frozen suspension of genetically modified autologous T cells in 5% dimethyl sulfoxide and human serum albumin is packed in a metal cassette and stored in the vapor phase of liquid nitrogen.

Efficacy Results in the ZUMA-2 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Efficacy-evaluable patients (n = 60)</th>
<th>Patients who underwent leukapheresis (ITT; n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>Objective response rate (95% CI)* 87% (75%-94%)</td>
<td>80% (69%-88%)</td>
</tr>
<tr>
<td>CR rate (95% CI)</td>
<td>62% (49%-74%)</td>
<td>55% (43%-67%)</td>
</tr>
<tr>
<td>PR rate (95% CI)</td>
<td>25% (15%-38%)</td>
<td>24% (15%-36%)</td>
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<tr>
<td>DOR</td>
<td>Median DOR, months (95% CI) NR (8.6-NE)</td>
<td>NR (8.6-NE)</td>
</tr>
<tr>
<td>Median DOR if best response is CR, months (95% CI) NR (13.6-NE)</td>
<td>NR (13.6-NE)</td>
<td></td>
</tr>
<tr>
<td>Median DOR if best response is PR, months (95% CI) 2.2 (1.5-5.1)</td>
<td>2.2 (1.5-5.1)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up for DOR, months* 8.6</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete remission; DOR, duration of response; ITT, intention-to-treat; NE, not estimable; NR, not reached; PR, partial remission.
*OR is measured from the date of the first objective response to the date of progression or death.
*At the time of the primary analysis.

Black Box Warning
- Cytokine release syndrome
- Neurologic toxicities

Other Warnings and Precautions
- Hypersensitivity reactions
- Severe infections
- Prolonged cytopenias
- Hypogammaglobulinemia
- Secondary malignancies
- Effects on ability to drive and use machines

Company: Kite Pharma, Inc

REFERENCE
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION.  

Approved across 5 indications spanning a wide range of multiple myeloma patients

INDICATIONS
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
DARZALEX FASPRO™: For a strong start to their treatment journey

~3 to 5 minute administration
• Subcutaneous injection is substantially faster than intravenous daratumumab.

The recommended dose of DARZALEX FASPRO™ is 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously over ~3 to 5 minutes. DARZALEX FASPRO™ is for subcutaneous use only. Do not administer intravenously.

See the Dosage and Administration section of the Prescribing Information for dosing considerations and dosing schedules for approved regimens.

See Important Safety Information below for hypersensitivity and administration reactions, pre-medication and post-medication requirements, and other important considerations for use of DARZALEX FASPRO™.

Efficacy consistent with intravenous daratumumab
• DARZALEX FASPRO™ demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients.
  - ORR was 41% (95% CI: 35%, 47%) for DARZALEX FASPRO™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259).
  - Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent.
  - In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with lenalidomide and dexamethasone (DrD) was evaluated in 65 patients with multiple myeloma who had received ≥3 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%).

Fewer systemic ARRs vs intravenous daratumumab
• Nearly 3x reduction in systemic administration-related reactions (ARRs) with DARZALEX FASPRO™ vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZALEX FASPRO™ had a systemic ARR of any grade vs 34% with intravenous daratumumab).
• Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™. See Important Safety Information for more details.

*For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.

In clinical trials of DARZALEX FASPRO™, DARZALEX® (daratumumab), and the Prescribing Information for DARZALEX®, the term “infusion reactions” was used instead of “systemic administration-related reactions.”

Get the latest data and information at darzalexhcp.com/faspro

Contact your Oncology Specialist to learn more about DARZALEX FASPRO™

Neutropenia
Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO™ until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO™, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia
Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of platelets.

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO™ can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use contraception during treatment with DARZALEX FASPRO™ and for 3 months after the last dose. The combination of DARZALEX FASPRO™ with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab binding to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO™. Type and screen patients prior to starting DARZALEX FASPRO™.

Interference with Determination of Complete Response
Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO™-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS
The most common adverse reaction (≥20%) with DARZALEX FASPRO™ monotherapy is: upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematological laboratory abnormalities (≥40%) with DARZALEX FASPRO™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.


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**Indications and Usage**

**Daratumumab** is indicated for the treatment of adult patients with multiple myeloma:
- in combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone in newly diagnosed and relapsed or refractory multiple myeloma.

**Warnings and Precautions**

**Hypersensitivity and Other Administration Reactions**
- Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with **Daratumumab**.

**Systemic Reactions**
- In a pooled safety population of 490 patients who received **Daratumumab** as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 3-4). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 3 minutes to 3.5 days).

**Local Reactions**
- In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%.

**Neutropenia**
- Daratumumab may increase neutropenia induced by background therapy. **Daratumumab** can cause severe or life-threatening neutropenia, including Grade 4 neutropenia.

**Thrombocytopenia**
- Daratumumab may increase thrombocytopenia induced by background therapy. **Daratumumab** can cause severe or life-threatening thrombocytopenia, including Grade 4 thrombocytopenia.

**Adverse Reactions**

**Drug Interactions**
- Daratumumab is a human IgG kappa monoclonal antibody that can be detected by assays used for the clinical monitoring of endogenous M-protein.

**Embryo-Fetal Toxicity**
- Daratumumab is a human IgG kappa monoclonal antibody that can be detected by assays used for the clinical monitoring of endogenous M-protein.

**Contraindications**
- Daratumumab is a human IgG kappa monoclonal antibody that can be detected by assays used for the clinical monitoring of endogenous M-protein.

**Adverse Reactions**

- **Hypersensitivity and Other Administration Reactions**
- **Neutropenia**
- **Thrombocytopenia**

**Clinical trials experience**

- **In combination with bortezomib, melphalan, and prednisone**
- **In combination with lenalidomide and dexamethasone**

**Drug interactions**

- **Daratumumab** is a human IgG kappa monoclonal antibody that can be detected by assays used for the clinical monitoring of endogenous M-protein.

**Use in specific populations**

- **Pregnancy**
- **Lactation**

**Reference**

- [see Dosage and Administration (2.3) in Full Prescribing Information](#)

**Pneumonias**

<table>
<thead>
<tr>
<th>Infections</th>
<th>N=67</th>
<th>Grades 3+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>13</td>
<td>1 (%)</td>
</tr>
<tr>
<td><strong>Lung and respiratory disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23%</td>
<td>17</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Cough includes cough, and productive cough.</td>
<td>22</td>
<td>3 (%)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
<td>3 (%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1 (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
<td>42</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
<td>49</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
<td>19</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-VMP (N=67).

**Table 2:** Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
<td>42</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
<td>49</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
<td>19</td>
</tr>
</tbody>
</table>

**Table 3:** Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>5 (%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3 (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5 (%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea includes dyspnea, and dyspnea exertional.</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough includes cough, and productive cough.</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5 (%)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9 (%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fatigue includes asthenia, and fatigue.
* Upper respiratory tract infection includes nasopharyngitis, pharyngitis, and viral pharyngitis
* Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia bacterial.
* Abdominal pain includes abdominal pain, and abdominal pain upper.
* Fatigue includes asthenia, and fatigue.
* Upper respiratory tract infection includes nasopharyngitis, viral pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection.
* Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
* Bronchitis includes bronchitis and bronchitis viral.
* Dyspnea includes dyspnea, and dyspnea exertional.
* Cough includes cough, and productive cough.
* Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) include:

**Recurrent/Refractory Multiple Myeloma**

**In Combination with Lenalidomide and Dexamethasone**

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, and dyspnea. The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 3 summarizes the adverse reactions in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.
**DARZALEX FASPRO™** (daratumumab and hyaluronidase-fihj) injection

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leucocytes</td>
<td>94  34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82  58</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86  9</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89  52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45  8</td>
</tr>
</tbody>
</table>

- *Denominator is based on the safety population treated with D-Rd (N=855).

**Monotherapy**

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than one patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 5 summarizes the adverse reactions in COLUMBA.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24  1*</td>
<td>22  1*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8  5</td>
<td>10  6*</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15  1*</td>
<td>11  0.4*</td>
</tr>
<tr>
<td>Nausea</td>
<td>8  0.4*</td>
<td>11  0.4*</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15  1*</td>
<td>16  2*</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>13  2*</td>
<td>34  5*</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13  0</td>
<td>13  1*</td>
</tr>
<tr>
<td>Chills</td>
<td>6  0.4*</td>
<td>12  1*</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10  2*</td>
<td>12  3*</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>9  1*</td>
<td>14  0</td>
</tr>
<tr>
<td>Cough</td>
<td>6  1*</td>
<td>11  1*</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

Treatment-emergent anti-daratumumab antibodies were tested in 451 patients treated with DARZALEX FASPRO as monotherapy or as part of a combination therapy. One patient (0.2%) who received DARZALEX FASPRO tested positive for anti-daratumumab antibodies and transient neutralizing antibodies. However, the incidence of antibody development might not have been reliably determined because the assays that were used have limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab.

Treatment-emergent anti-rHuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (16/192) of patients who received DARZALEX FASPRO as part of combination therapy. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposures. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

**Postmarketing Experience**

The following adverse reactions have been identified with use of intravenous daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Immune System:** Anaphylactic reaction

**Gastrointestinal:** Pancreatitis
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

Drug Interactions

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests

Indirect Coombs Test

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiotreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, administer non-cross-matched ABO/ RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

Use in Specific Populations

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, 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.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Deffer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 6 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embry-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human dose.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human dose.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

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

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness were observed based on age. Adverse reactions occurring at a higher frequency ≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspepsia, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions occurring at a higher frequency ≥2% difference) in patients ≥65 years of age included pneumonia.

Clinical studies of DARZALEX FASPRO as part of a combination therapy did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

References


Patient Counseling Information

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

Hypersensitivity and Other Administration Reactions

Advises patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for at least 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide is only available through a REMS program [see Use in Specific Populations].

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have had a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].
AS THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic continues to pose challenges, health care providers struggle with decisions on how to balance the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission with the need to treat patients’ underlying conditions. Because patients with chronic lymphocytic leukemia (CLL) have many risk factors that predispose them to a more severe course of COVID-19–related illness, including older age, higher prevalence of comorbidities, immunodeficiency from leukemia, and, possibly, immunosuppression from CLL treatments, this patient population is of particular concern.1

As part of a segment during an OncLive Peer Exchange®, a panel of hematologic cancer experts discussed how they are caring for their patients with CLL during the pandemic. They also discussed how treatment advances, many of which have the potential to transform the CLL landscape, may set standards should other pandemics emerge, a concern that has become particularly important as infectious disease experts warn that we may have entered an “era of pandemics.”2

“We know there are emerging data that show that patients receiving chemotherapy and patients with cancer on therapy in general are at a higher risk for poor outcomes [related to COVID-19],” said John N. Allan, MD, an assistant professor of medicine in the Division of Hematology and Medical Oncology at Weill Cornell Medicine in New York, New York.

Although the mortality data for patients with CLL who develop COVID-19 are alarming, Allan provided some reassurance. “I want to reiterate to patients and other physicians out there that just because a patient with CLL may get sick does not mean he or she is going to have horrible outcomes, though they are at risk for those things,” he said. He noted that many factors beyond CLL come into play and must be considered. “I think what we’ve shown time and time again with patients with COVID-19 is that age, hypertension, kidney disease, diabetes, obesity, and pulmonary disease are the things that really come together in a perfect storm. Patients are dying from overwhelming inflammatory conditions that occur with the virus that we are trying to grapple with and understand,” he said.

Protective measures must be taken and relayed to patients to help reduce the risk of SARS-CoV-2 transmission. “One way to mitigate risk is to encourage social distancing, use of masks, and hand hygiene, and really reiterate that,” Allen said. Using telemedicine when possible is also an option to minimize office visits. “There are a proportion of our patients who are on active observation, for example, who certainly can use telemedicine,” Nicole Lamanna, MD, said. “Patients can have local laboratory tests; there are services that some patients use that can have labs drawn at home, depending upon their insurance or capabilities, or they can go to a local lab and then have a telemedicine visit because they’ve been stable for years and they’re doing well otherwise.” Lamanna is an associate clinical professor of medicine at Columbia University Herbert Irving Comprehensive Cancer Center in New York, New York.

Additionally, outside influences, such as regional status concerning the number of cases as well as the potential therapeutic benefit of initiating treatments, are other case-by-case considerations. In the absence of symptoms, delaying intervention for patients who receive a diagnosis of CLL is common.3 “For patients with CLL I have found when we are in an exponential phase [of the pandemic], it is not a time when you want to be initiating treatment,” Allan said. “Instead, you want to minimize interaction and the immunosuppressive effects of some of these treatments and, essentially, if you do have a watch-and-wait patient, that’s when you push them out to telemedicine and using local labs.”

In a guideline article for treating patients with CLL during the SARS-CoV-2 pandemic,
Rossi et al estimate that the risk of contracting SARS-CoV-2 and developing COVID-19 outweighs the risk associated with delaying treatment until a time when the epidemic trajectory decreases.4

In contrast, if someone is sick and meets the standard treatment indications, Lamanna said the patient should be brought in to ensure they receive adequate treatment and avoid complications down the road. Mazyar Shadman, MD, MPH, agreed, saying, “Unfortunately, we have had a few patients who were not referred in a timely manner or decided to wait until the end of the pandemic. As a result, we had a more complicated situation in terms of starting treatment.” Shadman is an assistant professor at the University of Washington School of Medicine and an associate professor at Fred Hutchinson Cancer Research Center both in Seattle, Washington.

When treatment cannot be further delayed, guidelines recommend using systemic therapies that are less immunosuppressive and require fewer in-person visits (TABLE).4 During such times, the panelists agreed that Bruton tyrosine kinase inhibitors (BTKis) may be a particularly appealing option for patients requiring treatment because they are well tolerated, require minimal monitoring, and are taken orally. Options include ibrutinib (Imbruvica) and acalabrutinib (Calquence), which prolong progression-free and overall survival and have a lower risk of infection for patients compared with chemoimmunotherapy. Of note, ibrutinib does not allow for treatment holidays. For patients who are not candidates for BTKis, venetoclax (Venclexta) has a similar incidence of adverse effects, including rates for opportunistic infections; however, patients treated with the agent may require access to a hospital for the treatment of tumor lysis syndrome during the initial stages of therapy.4

Allan, Lamanna, and Shadman coauthored a study across 43 international centers that examined the outcomes of 198 patients with CLL who developed symptomatic COVID-19. The median age of the patients was 70.5 years. Of these patients, 90% required hospitalization. At a median follow-up of 16 days, the overall case fatality rate was 33%, and 25% remained admitted.1 The rates of hospital admission were similar between the treatment-naïve and treated patients, most of whom were treated with BTKis (76%).

Although mortality rates for all patients with CLL was high following hospital admission for COVID-19, CLL-directed treatment with BTKis did not negatively impact survival, with a case fatality rate of 34% versus 35% for those not on BTKis.1

In most of these patients, BTKi therapy was held at the time they received a diagnosis of COVID-19; however, a small subset of patients (n = 14) continued to receive BTKis and they had a lower case fatality rate (21%). These patients also appeared to require less frequent supplemental oxygen and mechanical ventilation, providing reassurance that continued BTKi use during the COVID-19 pandemic is unlikely to cause harm and may have benefit. However, data from larger studies will be needed for confirmation.1

In contrast, when COVID-19 cases are low, Allan said he may be more comfortable going back to more intensive approaches. “If I thought a patient would benefit from a VenG [venetoclax plus obinutuzumab (Gazyva)]-based approach pre-COVID-19, I’m comfortable doing this [when cases are low]. I feel like there’s a window of opportunity, though that could change if we start to see a [new] wave. You just have to pay attention to your caseload and what the virus rates are specific to your region,” Allan said.

Although the CLL COVID-19 study provided reassurance that BTKis do not negatively impact mortality, it is still unclear what effects other treatments alone or in combination have overall, especially more intensive regimens. Allan shared his experience in the clinic and noted that he has seen people on anti-CD20 treatment do well after developing COVID-19. “I’ve had patients seek treatment who have been on anti-CD20. They have recovered, though it took a little time to clear, but then they finally developed antibodies while being on a BTK inhibitor plus an anti-CD20 [therapy],” he said.

Lessons learned from the pandemic are likely to remain at the forefront, especially if SARS-CoV-2 transitions from an epidemic state to an endemic state with recurrent seasonal outbreaks. As such, Rossi et al caution that patients and doctors be prepared for surges and outbreaks to adapt care for those with CLL when stay-at-home orders are in place.4 Although recent data on the continued use of BTKis is encouraging, more data will modify approaches to care in the coming months and years.

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

Table: Recommendations for Patients With CLL Who Require Treatment During the COVID-19 Pandemic

<table>
<thead>
<tr>
<th>Patient scenario</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CLL requiring therapy</td>
<td>• Postpone initiation treatment if possible until case trajectory is decreasing. • Use systemic therapy that requires fewer clinic visits (ibrutinib, acalabrutinib, venetoclax).</td>
</tr>
<tr>
<td>Patients undergoing antileukemic therapy for CLL</td>
<td>• Test patients for SARS-CoV-2 infection 24-72 hours prior to start of treatment. • Frequent check-ins for clinical manifestations of COVID-19, including atypical symptoms</td>
</tr>
<tr>
<td>Patients on treatment for CLL with no evidence of COVID-19</td>
<td>• Continue treatment with targeted agents as in normal circumstances with the exception of anti-CD20 antibodies. • Infusions for patients receiving immunoglobulin replacement therapy will be less frequent or replaced with a subcutaneous formulation to be self-administered at home following training.</td>
</tr>
<tr>
<td>Patients on treatment for CLL who receive a diagnosis of COVID-19</td>
<td>• Hold therapy until recovery from COVID-19. • Resume if all conditions are met: - patient is asymptomatic for at least 48 hours - at least 14 days have elapsed from symptom start - at least 2 consecutive tests are negative and collected at least 1 week apart</td>
</tr>
</tbody>
</table>

Evidence Builds for ctDNA as a Potential Biomarker for MRD in Locally Advanced NSCLC

by ANITA T. SHAFFER

THE USE OF CIRCULATING tumor DNA (ctDNA) to analyze minimal residual disease (MRD) status in patients with lung cancer and other solid tumors is a rapidly developing field with the potential to further personalize treatment decisions about adjuvant therapy, according to Maximilian Diehn, MD, PhD.

In non–small cell lung cancer (NSCLC), ctDNA is strongly prognostic among patients with localized disease and may help clinicians determine whether consolidation therapy should be administered after surgery, Diehn said during a live virtual presentation at the 15th Annual New York Lung Cancers Symposium®.1

“This is one of the emerging applications of ctDNA that goes beyond just using this analyte for noninvasive tumor genotyping,” said Diehn, the vice chair of research and division chief of radiation and cancer biology at Stanford Cancer Institute and the Institute for Stem Cell Biology & Regenerative Medicine, both at Stanford University in California. “I think it’s one that is very close on the horizon that will transform how we manage [disease in] our patients.”1

Just as cell-free DNA leaks into the circulation as part of healthy biological functions, tumors also shed DNA that is mixed in with the patient’s germline DNA, said Diehn, who also is the CRK Faculty Scholar and an associate professor at Stanford. The ctDNA can be detected in blood plasma or serum samples, much like identifying tumor cells in tissue. “You can think of a blood draw from a patient as a very dilute tumor biopsy,” said Diehn.

Mutation-based assays for the detection of ctDNA can be used in either tumor-naïve or tumor-informed settings, Diehn said. Tumor-informed tests, designed for surveillance among patients known to have a mutation, have the highest analytical sensitivity of approximately 0.002%, whereas the tumor-naïve assays, used primarily for genotyping and early detection in people without prior knowledge of a mutation, have a detection limit of about 0.2%. An emerging ctDNA method that uses a methylation-based approach for tumor-naïve analysis also has a sensitivity of about 0.2%.1

As it stands now, the best option for MRD analysis is a mutation-based assay that uses a tumor-informed approach, according to Diehn. During the past several years, Diehn and colleagues have developed a next-generation sequencing–based ctDNA detection method called CAncer Personalized Profiling by deep Sequencing (CAPP-Seq). Regarding MRD analysis, clinicians can use CAPP-Seq to genotype tumors using tissue from patients with stage I to III disease or pretreatment plasma from stage III, and to sequence posttreatment plasma to determine MRD status. Diehn said the assay has a sensitivity of 0.002%.

In illustrating ctDNA’s potential use as a biomarker in NSCLC, Diehn noted findings from a study in 85 patients with localized disease that used CAPP-Seq technology. Investigators found that ctDNA was detected in 42%, 67%, and 88% of patients with stage I, II, and III disease, respectively, but the concentration of DNA shed by stage was low, particularly in stage I. The ctDNA concentration was higher in patients with more tumor volume. Additionally, the detection rate differed by histology, with 43% of adenocarcinoma versus 95% of nonadenocarcinoma samples with ctDNA.2

Although investigators have not yet been able to develop MRD assays for most solid...
cancers, Diehn believes the prospects of being able to do so hold great potential. “ctDNA appears to be a very promising approach for detecting MRD in a variety of solid tumors, including lung cancers,” he said. “If we could detect which patients have MRD after surgery for an early-stage lung cancer, we could potentially use that information to personalize further treatment. One could imagine that a patient who has no detectable ctDNA after surgery is likely cured and therefore may have little chance of benefiting from adjuvant therapy, whereas a patient who has detectable ctDNA is almost assuredly not cured by the surgeon because there's still evidence of tumor left and those patients might be the ideal group to which we would want to offer adjuvant therapy.”

The question of whether ctDNA can be used as a biomarker for MRD in this setting has generated considerable debate, Diehn said. Some experts argue that ctDNA analyses fail to detect residual disease in many patients and that those who are ctDNA-positive have too much disease burden to benefit from the testing. On the other hand, other investigators say the assays are sufficiently sensitive and that some patients who are MRD-positive using these methods can gain from treatment.

Randomized trials to evaluate these competing hypotheses are getting started, “but it will be years before they read out,” Diehn said. In the meantime, investigators studied the impact of ctDNA in a clinical scenario in stage III NSCLC in light of findings in the landmark phase 3 PACIFIC trial (NCT02125461). The study evaluated the PD-L1 inhibitor durvalumab (Imfinzi) versus placebo in patients with stage III unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy (CRT). Progression-free survival (PFS) findings from the study prompted the FDA to approve durvalumab in this patient population in February 2018.

In updated findings for the overall study population, durvalumab therapy resulted in a median PFS of 17.2 months (95% CI, 13.1-23.9) compared with 5.6 months (95% CI, 4.6-7.7) in the placebo group, which translated into a 49% reduction in the risk of disease progression or death (HR, 0.51; 95% CI, 0.41-0.63). However, Diehn said the PFS curves indicate that although some patients were cured by durvalumab therapy and others were cured by CRT without further treatment, the largest group of patients did not derive benefit from consolidation therapy.

To test whether ctDNA could predict which patients would benefit from adjuvant immunotherapy in this setting, Diehn and colleagues conducted a retrospective study of 62 patients with stage III NSCLC: 37 who received CRT without further treatment and 25 who received CRT followed by consolidation with an immune checkpoint inhibitor (ICI). Patients with negative ctDNA after CRT had better outcomes and similar responses whether or not they received consolidation with an ICI, Diehn said, which suggests that this group would not benefit from further treatment. Moreover, 1 patient with detectable ctDNA prior to CRT, who was ctDNA-negative after CRT and received an ICI, went on to develop grade 5 drug-induced pneumonitis. Diehn said the autopsy showed no residual cancer.

Analyzing ctDNA could provide clues about whom not to treat with adjuvant therapy, he noted.

Meanwhile, patients without a ctDNA response during consolidation ICI therapy also did not seem to benefit from continued treatment, suggesting they had developed intrinsic resistance, Diehn pointed out. The “most exciting” outcomes were among patients who had detectable ctDNA after CRT and who achieved negative ctDNA after ICI therapy. “These are the ones who are really deriving benefit from consolidation immunotherapy,” he said.

Although Diehn focused on findings from his research group during the presentation, he said other investigators using different assays had similarly demonstrated that ctDNA MRD has strong prognostic power in studies involving more than 200 patients with localized NSCLC.

One signal of potential clinical adoption of ctDNA assays for MRD assessment came in October 2020 when the Centers for Medicare & Medicaid Services issued a proposed local coverage determination (LCD) for validated tests able to detect molecular recurrence or progression before it is evident through clinical or radiographical evaluation. The LCD, which was open for comment until November 22, 2020, would cover patients with advanced cancer or a personal history of cancer, including solid tumors and hematologic malignancies.

“I believe the glass is half-full,” Diehn said. “We can use ctDNA MRD to identify patients who might be the best candidates for consolidation or adjuvant therapy and this would allow us to personalize additional therapy in the early-stage patients in a way we are currently not doing.”

**REFERENCES**

THE EVIDENCE TO
FIGHT ON
with ONIVYDE®

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

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

**LIMITATION OF USE**
ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

**IMPORTANT SAFETY INFORMATION**

**WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA**

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

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

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

**WARNINGS AND PRECAUTIONS**

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

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

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

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

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

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

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

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


FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE1

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

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For more information, visit ONIVYDEinfo.com.

ônivyde®

(irinotecan liposome injection)
ONIVYDE® (irinotecan liposome injection) for intravenous use
Initial U.S. Approval: 1996

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

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

Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas (see Clinical Studies, 14).

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

5. WARNINGS AND PRECAUTIONS
5.1 Severe Neutropenia: ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1,117 patients in the ONIVYDE®/5-FU/LV arm and 1,174 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

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

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1,500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1,500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosage and Administration, 2.2).

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

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

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

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

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

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

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

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

6.1 Clinical Trials Experience
The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/5-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the 5-FU/LV arm.

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

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
An individual patient may experience both early- and late-onset diarrhea. ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas.

**INDICATIONS AND USAGE**

**BRIEF SUMMARY:** refer to full Prescribing Information for ONIVYDE®.

Severe or life-threatening neutropenic fever or sepsis treatment of patients with metastatic adenocarcinoma of the pancreas.

Limitation of Use: ONIVYDE® is not indicated as a single agent for the progression following gemcitabine-based therapy.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3 or 4 early-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV; the most common 

**WARNINGS AND PRECAUTIONS**

5.1 Severe Neutropenia:

- Severe or life-threatening neutropenia and severe diarrhea followed one of two patterns: late-onset (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks and early-onset (ONIVYDE®/5-FU/LV; n=147). Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² every 3 weeks.

In the ONIVYDE®/5-FU/LV arm, the incidence of Grade 3 or 4 neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia. The most common adverse reactions were observed between these patients and younger patients.

5.4 Severe Hypersensitivity Reaction:

- Severe or life-threatening diarrhea of any severity. (see Cholinergic Reactions, 6.1)

Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, blood urea nitrogen ≤40 mg/dL, and creatinine ≤1.5 mg/dL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy, Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women.

Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

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

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

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

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

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

10 OVERDOSAGE

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

**Table 2: Adverse Reactions with Higher Incidence**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE®/5-FU/LV n=117</th>
<th>5-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Intravenous catheter-related infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
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<td>Weight loss</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Dehydration</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Cholinergic Reactions: ONIVYDE® can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE®-treated patients. Six of these 12 patients received atropine and in 1 of the patients, atropine was administered for cholinergic symptoms other than diarrhea.

Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE® administration, were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV.

The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥2% difference Grades 1–4 [any] or ≥5% difference Grades 3–4 [severe]) according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/5-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. Hematologic: anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). Hepatic: increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%). Metabolic: hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%). Renal: increased creatinine (any 18%, 13%; severe 0%, 0%).
Chemoimmunotherapy Remains Best Choice for Some PD-L1–High Lung Cancers

by JASON HARRIS

ALTHOUGH IMMUNOTHERAPY ALONE is the right therapy for most patients with lung cancer expressing PD-L1 of 50% or greater, chemoimmunotherapy may be the more appropriate choice for those at risk for cancer-related morbidity with early progressive disease, Nasser H. Hanna, MD, said in a presentation at the 15th Annual New York Lung Cancers Symposium®.

Clinical evidence has shown that omitting chemotherapy in the front line results in earlier disease progression for some patients with non-small cell lung cancer (NSCLC), even those with a PD-L1 tumor proportion score (TPS) of at least 50%.

“This might be a patient with highly symptomatic disease, or a patient with bulky disease, or a patient whose performance status is okay but the trajectory is not looking good,” said Hanna, the Tom and Julie Wood Family Foundation Professor of Lung Cancer Clinical Research at Indiana University School of Medicine. “So you want to ensure that they don’t have early progression, or at least reduce the likelihood. That’s the patient [for whom] I think I would add chemotherapy to their immunotherapy.”

In a review of studies, Hanna identified data from trials comparing immune checkpoint inhibitors (ICIs) including pembrolizumab (Keytruda), nivolumab (Opdivo), and atezolizumab (Tecentriq) plus chemotherapy versus chemotherapy alone, that demonstrated a marked benefit for patients with PD-L1-high lung cancer. However, although efficacy data favor chemoimmunotherapy in these patients, questions still exist surrounding the use of ICIs upfront without chemotherapy in this patient population.

CHEMIOIMMUNOTHERAPY DEMONSTRATES BENEFIT IN PD-L1–HIGH POPULATION

In KEYNOTE-189 (NCT02578680), investigators evaluated platinum-based chemotherapy plus pemetrexed with or without pembrolizumab in 616 patients with metastatic, nonsquamous NSCLC without sensitizing EGFR or ALK mutations. Patients in the placebo group who had verified disease progression were allowed to cross over to the pembrolizumab arm.1

After a median follow-up of 10.5 months, the 12-month overall survival (OS) rate favored the pembrolizumab combination among those with a PD-L1 TPS of 50% or greater (73.0% vs 48.1%; HR, 0.42; 95% CI, 0.26-0.68).1 These patients derived a greater benefit than the intention-to-treat (ITT) population; estimated 12-month OS rates were 69.2% in the pembrolizumab combination group versus 49.4% in the placebo combination group (HR, 0.49; 95% CI, 0.38-0.64; \( P < .001 \)).

In updated results published in May 2020, the median OS was 22.0 months (95% CI, 19.5-25.2) in the pembrolizumab group versus 10.7 months (95% CI, 8.7-13.6) in the placebo arm (HR, 0.56; 95% CI, 0.45-0.70). Notably, in the population of patients with a PD-L1 TPS of at least 50%, the median OS was not reached (NR) with the pembrolizumab combination (95% CI, 20.4-NR) versus 10.1 months (95% CI, 7.5-13.6) in the placebo group versus 10.7 months (95% CI, 8.7-13.6) in patients receiving carboplatin plus nab-paclitaxel alone (HR, 0.48; 95% CI, 0.29-0.81).4

Finally, interim OS analysis from IMPower150 (NCT02366143) showed that the combination of atezolizumab, bevacizumab (Avastin), carboplatin, and paclitaxel (ABCP) extended survival compared with bevacizumab plus carboplatin and paclitaxel (ACP) in patients with untreated nonsquamous metastatic NSCLC. In the ITT wild-type population, the median OS was 19.2 months for the ABCP arm compared with 14.7 months in the ACP arm (HR, 0.78; 95% CI, 0.64-0.96; \( P = .02 \)). Median OS also favored the quadruplet in the PD-L1-high subset (25.2 vs 15.0 months; HR, 0.70; 95% CI, 0.43-1.13).5,6

and what you’ll see is a lack of detriment in early survival when chemotherapy was given to all patients.”

In squamous cell NSCLC, initial findings from the phase 3 IMPower130 trial (NCT02367781) presented in 2018 showed that adding atezolizumab to carboplatin and nab-paclitaxel (Abraxane) improved progression-free survival and OS among patients with high PD-L1 expression.3

“Once again, the magnitude of difference favoring the addition of atezolizumab was seen in those patients who had high PD-L1 scores,” Hanna said.

Final OS data from IMPower131 (NCT02367794) further supported the observed benefit with the chemoimmunotherapy combination. Among patients with high PD-L1 expression (≥ 50% staining on tumor cells or ≥ 10% tumor-infiltrating immune cells), the median OS was 23.4 months (95% CI, 17.8-not evaluable) with the atezolizumab triplet compared with 10.2 months (95% CI, 7.1-17.5) in patients receiving carboplatin plus nab-paclitaxel alone (HR, 0.48; 95% CI, 0.29-0.81).4

**TABLE.** Overall Survival Results for Patients With PD-L1–High Lung Cancer²⁻⁹

<table>
<thead>
<tr>
<th>Overall survival rate</th>
<th>KEYNOTE-189</th>
<th>CheckMate 227</th>
<th>CheckMate 9LA</th>
<th>KEYNOTE-024</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>73.3%</td>
<td>67%</td>
<td>70%</td>
<td>70.3%</td>
</tr>
<tr>
<td>24 months</td>
<td>51.9%</td>
<td>48%</td>
<td>Not reported</td>
<td>51.5%</td>
</tr>
</tbody>
</table>

**Nasser H. Hanna, MD**
“Giving chemotherapy with immunotherapy for at least the beginning of treatment was the rationale behind CheckMate 9LA,” Hanna said. “It was thought that there may be a detriment in early outcomes if you don’t give chemotherapy and you simply gave immunotherapy.”

CheckMate 9LA (NCT03215706) randomized patients to either chemotherapy alone or chemotherapy for 2 cycles in combination with nivolumab plus ipilimumab (Yervoy). The OS rate in the ITT population was 63% at 12 months compared with 70% (HR, 0.66; 95% CI, 0.44-0.99) in those patients with PD-L1 expression of at least 50%.

FINDING CLEARER ANSWERS IN ECOG/ACRIN 5163

Hanna said that although OS at 1 and 2 years was similar regardless of treatment strategy in 4 key trials (TABLE 3-7), there are still unanswered questions for patients with high PD-L1 expression in terms of optimal sequencing strategies. The existing data suggest there is a role for ICIs plus chemotherapy for some patients. There is, however, relatively little research comparing ICIs alone versus ICIs plus chemotherapy, Hanna said, noting that it is the early part of the survival curve that is cause for concern.

“Should we start patients with chemotherapy/IO [immunotherapy] or can we give them IO alone? And if we do give them IO alone, do we abandon the IO when they progress, or can we continue the IO and simply add chemotherapy? This is a really important sequencing question, [the answer to which] I think will greatly help us,” Hanna said.

Investigators are looking at data from the phase 3 ECOG/ACRIN 5163 study (NCT03793179) to help clarify how best to administer chemoimmunotherapy in this patient population.

Patients with stage IV nonsquamous NSCLC will be randomized to 1 of 3 treatment arms: first-line treatment with pembrolizumab monotherapy followed by pemetrexed and carboplatin after disease progression; the same regimen plus pembrolizumab in the second line; or pembrolizumab plus pemetrexed and carboplatin followed by maintenance therapy with pembrolizumab and pemetrexed.

“This is a really important sequencing question which will, I think, greatly help us,” Hanna said. “When we look at this study, we’ll pay close attention to the [subset with] PD-L1 greater than 50%, which would be anticipated to be half of the patients in this PD-L1-positive study population.”

REFERENCES

3. Cappuzzo F, McCleod M, Hussein M, et al. IMpower130: progression-free survival (PFS) and safety analysis from a randomised phase III study of carboplatin + nab-paclitaxel (CP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC. Ann Oncol. 2018;29(suppl 8):vii42-vii43. doi:10.1093/annonc/mdy424.065
AT THE BEGINNING OF HIS CAREER as a medical oncologist in the 1990s, lung cancer specialist Rogerio C. Lilenbaum, MD, was squarely focused on diagnosing and treating his patients while translating emerging clinical research into practice.

Now, as director and senior physician executive of the Banner MD Anderson Cancer Center, headquartered in Gilbert, Arizona, one of his priorities is fostering a patient-centered experience from an institutional perspective—and his definition of the term is far broader than “this automatic reflex of thinking about welcoming patients or being nice to patients,” which he calls “the minimum expected of everyone in health care.” Instead, he seeks to deliver consistent and timely quality care that encompasses clinical, operational, financial, and cultural considerations.

“It’s the totality of the experience,” Lilenbaum said in an interview with OncologyLive®. Cancer centers, for example, think of access as being “a business opportunity” rather than part of a patient-centered experience, he noted. “If you see patients quickly, they’ll come to you, as opposed to having to wait a week or 2 to go to a better center. That’s how many people, right or wrong, choose where they go [for treatment].

“And yet at the end of the day, it really is unconscionable to keep someone who was just given a diagnosis of cancer waiting weeks to see a physician,” Lilenbaum said. “And that’s a humanistic responsibility. It’s not about market share. It’s the way we all expect to be treated under these circumstances.”

Lilenbaum will bring his real-world blend of patient-centered oncology into focus from February 5 to 7, 2021, at the 18th Annual Winter Lung Cancer Conference®. He is serving as a conference cochair along with Mark A. Socinski, MD, executive medical director of AdventHealth Cancer Institute in Orlando, Florida; and Julie R. Brahmer, MD, MSc, director of the Thoracic Oncology Program and professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland. The conference, hosted by Physicians’ Education Resource® LLC (PER®), will be held as a virtual meeting.

The hallmark of the conference, Lilenbaum said, will be the opportunity not only to learn about the most impactful recent trial and study findings but to hear opinions and analysis from leading lung cancer experts. Topics include discussions of when to stop immunotherapy, the role of palliative care in patients with thoracic malignancies, and strategies for treating patients with immunotherapy while molecular testing results are pending.

A special keynote program on addressing critical clinical issues in lung cancer will be held during the opening session on February 5 at 7:55 PM. According to Lilenbaum, one of the most important discussions during that session will center around the optimal use of targeted therapy for patients with non–small cell lung cancer (NSCLC).

Lilenbaum’s concerns involve the uptake of biomarker testing. Although molecular testing is recommended for all patients with advanced nonsquamous NSCLC and certain populations with squamous cell disease, rates of adoption vary depending on the aberration in the United States and in other countries. Whereas testing for EGFR mutations
and ALK translocations has reached as high as 87% and 69%, respectively, in some US areas, testing for ROSI alterations was only at 28% in one study.1

“Are we testing everyone for all the actionable mutations? And are we treating those patients according to evidence-based algorithms and guidelines?” Lilenbaum asked. “This may seem a very obvious thing to do, but it’s far from common practice. Testing, in this day and age, still is somewhat erratic. It’s not pervasive or as generalized as it should be. And then even within each category—EGFR, ALK, ROSI, RET, BRAF/V600E—the information about how to best manage those patients is not always within the domain of the general oncologist.”

The introduction of immune checkpoint inhibitors (ICIs) into the treatment paradigm has further complicated therapeutic strategies, illustrating the need for a greater understanding of which patients would most benefit from ICIs, Lilenbaum continued.

Heather A. Wakelee, MD, a professor of medicine and faculty director of the Stanford Cancer Clinical Trials office at Stanford University Medical Center in California and president elect of the International Association for the Study of Lung Cancer, agreed with the need to improve patient selection approaches.

“It is critical to wait for full information about a newly diagnosed lung cancer before starting a patient on treatment,” said Wakelee, who will serve as a cochair of the 22nd Annual International Lung Cancer Congress4 in July 2021. “PD-L1 results come back very quickly, and the molecular results for EGFR, ALK, ROSI, and BRAF [alterations] and so on can take several weeks. Patients with molecular driver mutations like EGFR and ALK are much better treated with targeted therapy and do poorly on immunotherapy. If immunotherapy is started too quickly, it can complicate use of targeted therapy because of increased toxicity risks. So it is much better to wait for full information so a patient can be started on the best therapy instead of rushing to start immunotherapy when only some information [on PD-L1] is back.”

It would be a significant step forward to have additional biomarkers beyond PD-L1 expression levels for recommending patients with NSCLC for ICI therapy, Lilenbaum stated. “The question is, how do we identify patients who truly benefit from checkpoint inhibitors beyond just the PD-L1 marker?” he asked. “We’ve seen now, years into this research, that in some patients, the benefit is nothing short of extraordinary. And in other patients, it’s fairly modest. Yes, PD-L1 is a marker that can help ascertain that magnitude of benefit, but it’s far from perfect. I think we need additional predictive factors to justify the cost and the toxicity of these agents.”

**EARLY-STAGE IMMUNOTHERAPY**

At the same time, Lilenbaum said, the PD-L1 inhibitor durvalumab (Imfinzi) appears to be underused in the consolidation setting, a problem he called “baffling.” In February 2018, the FDA approved durvalumab for patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemoradiation therapy (cCRT).2

The decision, which represented a new standard in this disease setting, was based on findings from the phase 3 PACIFIC trial (NCT02125461) in which 713 patients in this population who had received at least 2 cycles of cCRT were randomized 2:1 to receive

---

**FIGURE 1. Snapshot of Guideline-Based Consolidation Immunotherapy Use in Stage III NSCLC4 Survey of 150 US Medical Oncologists**

<table>
<thead>
<tr>
<th>Reasons for not recommending immunotherapy</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient refused due to affordability, AEs, and/or other reason</td>
<td>21%</td>
</tr>
<tr>
<td>Progression after cCRT</td>
<td>20%</td>
</tr>
<tr>
<td>Poor PS after cCRT</td>
<td>17%</td>
</tr>
<tr>
<td>PD-L1 negative (&lt; 1%)</td>
<td>13%</td>
</tr>
<tr>
<td>Targetable mutation identified</td>
<td>10%</td>
</tr>
<tr>
<td>Failed to complete CRT</td>
<td>8%</td>
</tr>
<tr>
<td>Payer coverage challenges</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons patients declined recommended immunotherapy</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Treatment fatigue/patient refusal of any treatment</td>
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</tr>
<tr>
<td>Insurance coverage difficulty</td>
<td>19%</td>
</tr>
<tr>
<td>Out-of-pocket costs associated with treatment/travel</td>
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</tr>
<tr>
<td>Prefer a different treatment option</td>
<td>12%</td>
</tr>
<tr>
<td>Transportation/caregiver difficulties</td>
<td>10%</td>
</tr>
<tr>
<td>Inconvenient dosing schedule/work interference</td>
<td>10%</td>
</tr>
</tbody>
</table>

AEs, adverse effects; cCRT, concurrent chemoradiotherapy; CRT, chemoradiation therapy; PS, performance score.

**FIGURE 2. Patient Population in ADAURA Trial1**

<table>
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<tr>
<th>AJCC stage</th>
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<tr>
<td>IB</td>
<td>34%</td>
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<tr>
<td>II</td>
<td>32%</td>
</tr>
<tr>
<td>IIA</td>
<td>34%</td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee on Cancer.

*Patients in both arms of the trial who received either osimertinib or placebo.

Figure is rounded.
durvalumab or placebo. At a prespecified interim analysis, median overall survival (OS) was not reached (NR) among participants treated with durvalumab (95% CI, 34.7 months-NR) compared with 28.7 months (95% CI, 22.9-NR) for those who received placebo, translating into a hazard ratio favoring durvalumab of 0.68 (95% CI, 0.53-0.87; \( P = .0025 \)). Median progression-free survival was 16.8 months (95% CI, 13.0-18.10) with durvalumab versus 5.5 months (95% CI, 4.6-7.8) with placebo (HR, 0.52; 95% CI, 0.42-0.65; \( P < .0001 \)).

In updated findings reported after a median follow-up of 33.3 months, the median OS with durvalumab was still NR (95% CI, 38.4-NR) versus 29.1 months (95% CI, 22.1-35.1) with placebo (stratified HR, 0.69; 95% CI, 0.55-0.86). The OS rates with durvalumab compared with placebo, respectively, were 83.1% versus 74.6% at 12 months, 66.3% versus 55.3% at 24 months, and 57.0% versus 43.5% at 36 months.1

“We have unequivocal data that 1 checkpoint inhibitor, durvalumab, improves outcomes” for patients with stage III unresectable disease, Lilenbaum said. “And yet, to the best of my knowledge, the utilization of that strategy is not as high as it should be.”

The management of therapeutic choices for this patient population is complex, Lilenbaum acknowledged. “In order to get to the durvalumab piece, [the patient] has to have received concomitant chemotherapy and radiation and not everybody does.” Nevertheless, he said, “it surprises me at times that powerful data like these are still not applied more widely.”

Findings from a recent survey reflect Lilenbaum’s concerns. The percentage of patients with unresectable stage III NSCLC who received guideline-recommended cCRT as initial therapy was an average of 48% and, of those, only 55% subsequently received immunotherapy, according to responses from 150 US medical oncologists published in October 2020 in *JCO Oncology Practice* (FIGURE 1).4

**ADJUVANT THERAPY BREAKTHROUGH**

Looking forward, Lilenbaum anticipates that molecularly targeted therapies as well as immunotherapies will be used earlier in the NSCLC treatment timeline. Recent clinical data for osimertinib (Tagrisso) in patients with completely resected *EGFR*-positive stage earlier-stage disease represent “a breakthrough that will change the way we do adjuvant treatment,” Lilenbaum said.

In the phase 3 ADAURA trial (NCT02511106), 682 patients with stage II to IIIA disease were randomized 1:1 to receive osimertinib or placebo (FIGURE 2). At 24 months, 89% of participants treated with osimertinib (95% CI, 85%-92%) were alive and disease-free versus 52% of those who received a placebo (95% CI, 46%-58%), which translated to an overall hazard ratio for disease recurrence or death for osimertinib therapy of 0.20 (99.12% CI, 0.14-0.30; \( P < .001 \)).

The FDA has granted a priority review for a supplemental new drug application for osimertinib as adjuvant treatment for patients with early-stage *EGFR*-mutant NSCLC after complete tumor resection. A decision is expected during the first quarter of 2021, according to AstraZeneca, the company developing the drug.6

“I think we’re going to see similar data for other molecular alterations,” Lilenbaum said. “And more importantly, we will see data for immunotherapy in the early-stage settings. How you apply the knowledge that we’ve acquired in late-stage disease to early-stage disease is one of the most potentially impactful areas of research because in early stage, what you’re doing is beyond prolonging life, you’re increasing the cure rate. And that’s what we want to see.”

**BROADER ROLE IN CANCER CARE**

Throughout his career in the lung cancer field, Lilenbaum has often focused on helping to define best practices and optimal treatment choices. He has participated in crafting National Comprehensive Cancer Network guidelines for NSCLC and malignant pleural mesothelioma as well as American College of Chest Physician recommendations for the use of chemotherapy in patients with stage IV NSCLC.

“I believe in the power of guidelines,” Lilenbaum said, adding that such recommendations should be routinely used in clinical practice. Beyond that, guidelines are incorporated into clinical pathways that are integrated into electronic medical records. “Clinical pathways address, to some extent, heterogeneity in how people choose to treat certain diseases, and bring some measure of consistency in how a certain practice decides to treat a group of patients.”

Lilenbaum’s path to his administrative role at Banner MD Anderson spans 2 continents. His early years were spent in his native Brazil. After earning his medical degree from the Federal University of the State of Rio de Janeiro School of Medicine and Surgery and starting his training in the late 1980s, he realized he wanted to become a medical oncologist. He came to the United States...
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• Navigating options for first-line immunotherapy-based regimens in metastatic NSCLC
• Application of consolidation immunotherapy in locally advanced NSCLC
• Current approaches with surgery and radiation oncology in patients with thoracic malignancies

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CONTINUED FROM PAGE 36

in the mid 1990s to pursue opportunities in cancer care.

“I enjoyed not only the practice of medicine in the United States, but also the academic component, specifically the opportunity to be involved in clinical research,” Lilenbaum said. “By the time I was finishing my fellowship, I really couldn’t see myself in any other place. And I was very fortunate to have outstanding mentors who opened a lot of doors and opportunities for me. So I had an early entry into the world of lung cancer investigation and research.”

The attraction to oncology at that point was the development of chemotherapy drugs that offered promise for the treatment of patients with NSCLC. “This was a disease that up until the early to mid ‘90s had essentially 1 or 2 regimens that had shown some efficacy, and by the way, horrendous toxicity as well,” Lilenbaum noted. “The new drugs at the time seemed to provide greater benefit, and lower toxicities.”

At the outset of his career, Lilenbaum spent 80% or more of his time seeing patients. After approximately 15 years of an active clinical practice, however, he decided he wanted to find ways to influence how treatment is delivered in broader terms, and then take that experience into organizations that were creating a comprehensive, integrated cancer care delivery system.

“In many ways, it’s more challenging than clinical care or clinical research, but no less important,” said Lilenbaum, who now sees patients less than 10% of the time. Part of the challenge is learning the skills needed to be an administrator.

“Certainly, physicians in my generation were not trained for this,” Lilenbaum said. “We don’t necessarily graduate from a fellowship with organization skills or leadership skills. If anything, we’re trained to acquire a certain body of knowledge and make decisions independently on behalf of the individual in front of you who happens to be a patient at the time.”

Lilenbaum’s opportunity to translate his knowledge in a more foundational way came when he was recruited to be chief medical officer for the Yale Cancer Center and Smilow Cancer Hospital at Yale New Haven Health in Connecticut, where he oversaw clinical programs and clinical operations, as well as quality, safety, and network development for the cancer program. Working with some of the country’s top practitioners in cancer care propelled him forward.

In February 2020, Lilenbaum began his new role as director and senior physician executive of a group of facilities at Banner MD Anderson Cancer Center,’ where instilling the patient-centered experience throughout the organization is one of his main goals. “People need comfort, support, guidance, because they are overwhelmed by what’s going on with them,” he said.

To illustrate his point, Lilenbaum related an anecdote from a colleague at another center who was able to obtain VIP treatment for her elderly father when he was diagnosed with cancer. Her father saw multiple doctors and received an infusion on the same day. The visit overall was exhausting but appeared to be a complete success; the marathon day wrapped up around 7 PM.

“But when they left the facility, the valet guy was no longer there,” Lilenbaum recalled. “And they could not find the keys to their car. They spent another 45 minutes trying to find the keys. That particular moment, in a way, tainted their entire experience of what until then had been an excellent day.”

The challenge at Banner MD Anderson is fully integrated treatment across about 10 facilities in Arizona and Colorado. In short, regardless of where patients are treated, they should receive the same level of treatment and have a similar experience.

“Different allocation of resources is expected. For example, you’re not going to have a bone marrow program in every one of your facilities,” Lilenbaum said. “But basic services need to be widely available. To create that alignment, to create that sense that it’s all one experience, is a pretty challenging goal from an administrative and financial perspective.”

COPING WITH COVID-19

Like all cancer centers in America, Banner Health has been forced to meet the challenge of how to maintain care in the face of coronavirus disease 2019 (COVID-19). Banner’s Arizona facilities were put to the test, treating approximately 45% of all patients with COVID-19 in the state, Lilenbaum pointed out. By taking numerous preventive measures, they were able to keep the cancer center campus 100% free of the virus.

“That was a spectacular win for our patients and our staff,” Lilenbaum said. “Patients who came in and were found to have COVID-19 were transferred to other facilities, and we would take other patients from those facilities to make sure that we were all managing the bed utilization appropriately. But we did not want to have patients with COVID-19 on this campus [in Gilbert, Arizona] because this is where we have our most vulnerable, at-risk patients.”

“We also started to test our patients early on before certain types of cancer intervention,” he explained. “So we knew that if they were to be subjected to interventions that might diminish their resistance or increase their vulnerability to the virus, we would at least know that they were negative ahead of time. Then we started to test high-risk staff members, so that we knew that they could interact with those patients.”

Banner MD Anderson was also included in the first wave of telehealth use, he noted, allowing staff to become comfortable with the process from the outset and enabling them to treat patients with cancer without bringing them on campus unnecessarily. Lilenbaum predicted that insurance companies might tighten up on reimbursements for telehealth, but now that the technology has been put to use, there is no turning back.

“I don’t know that we will have as much freedom and flexibility as we had during the peak of the pandemic, but I think everybody realizes that this is a technology that is here to stay,” he said.
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  - Locally advanced or metastatic NSCLC, stage III or IV

✓ At least one resectable tumor for TIL generation
✓ 18 years old or older
✓ ECOG PS 0-1

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Next-Generation Cytotoxic Therapy Moves Forward in mCRPC

by JASON HARRIS

VERU-111, A NEXT-GENERATION form of chemotherapy, has shown promising signs of efficacy as a treatment option for men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed while receiving androgen receptor (AR)-targeting therapy.

Investigators are planning a phase 3 trial that will test VERU-111 against an alternative AR-blocking agent in men with mCRPC who have developed resistance to abiraterone acetate (Zytiga) or enzalutamide (Xtandi), which typically are administered in this treatment setting (FIGURE). Veru Inc, the company developing the agent, plans to launch the trial during the first quarter of 2021, pending discussions with the FDA.

VERU-111 is an oral therapy that binds to the colchicine binding site on the microtubule to crosslink α and β tubulin, thus inhibiting microtubule polymerization. Preclinical findings show that the agent induces apoptosis in taxane-resistant and enzalutamide-resistant CRPC cell lines.

Findings from a phase 1b/2 study (NCT03752099) showed that daily chronic administration of VERU-111 was feasible and safe in men with previously treated mCRPC, according to data presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020.

Investigators enrolled 39 patients across 7 sites in the United States. Eligible men with mCRPC had to have received 1 prior AR-targeted therapy; those who had received 1 line of taxane-based chemotherapy for mCRPC were included. The median age of participants was 74 years (range, 61-92), the median Gleason score was 8 (range, 5-10), and 95% had ECOG performance status scores of 0 or 1.

In the first part of the study, investigators tested a 2-part dosing schedule using a standard 3 x 3 dose-escalation strategy across 10 dosing levels ranging from 4.5 mg to 81 mg daily. The recommended phase 2 dose was established as 63 mg daily.

Outcomes were reported for a subset of 10 men who received VERU-111 monotherapy continuously at the recommended dose for 4 or more cycles. Of these patients, 6 had a decrease in prostate-specific antigen (PSA) levels, including 4 with a decrease of 30% or more and 2 with a decrease of 50% or more. The best objective tumor response comprised 2 patients with partial responses and 8 with stable disease. The median duration of treatment without radiographic progression was more than 11 months (range, 6-17) and half of the 10 men remained on study therapy at the time of presentation.

Additionally, investigators presented results from 1 patient, an 88-year-old man with Gleason 9, node-only mCRPC who had previously received sipuleucel-T (Provenge), enzalutamide, and abiraterone. After VERU-111 therapy, a CT scan showed a 33% decrease in size to a nonpathologic node. Further, the patient experienced a 63% reduction in PSA level within the first cycle of treatment and remained in the study for over 16 months.

In the safety population of 25 patients who had been treated with the recommended dose for at least 1 cycle, the most frequently observed drug-related adverse effects (AEs) included diarrhea (56%), nausea (24%), and decreased appetite, fatigue, dysgeusia, and weight loss (all, 12%). Most AEs were of grade 1 or 2 severity. An

FIGURE. Proposed Phase 3 Trial of VERU-111 in mCRPC

ADT, androgen-deprivation therapy; AR, androgen receptor; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.
instance of fatigue that was resolved with a dose reduction was the only drug-related AE of grade 3 or worse at the 63-mg dose. Investigators did not record any reports of neurotoxicity in the study and no incidence of neutropenia at the 63-mg dosing level.²

THERAPY MAY FILL UNMET NEEDS

The trial’s early findings are generating interest among experts in prostate cancer. “One impressive aspect of this study was the PSA declines of 50% or more,” said Neal D. Shore, MD, medical director of Carolina Urologic Research Center in Myrtle Beach, South Carolina, in an interview with OncologyLive⁶.

Shore said VERU-111’s oral route of administration could make it an attractive choice compared with traditional taxanes such as docetaxel and cabazitaxel (Jevtana), which are given intravenously. “Especially during the time of a pandemic, one recognizes the advantage for using an oral medication not requiring a clinic visit for administration,” he said. “The oral-based delivery may also appeal to clinicians who are not offering infusions within their clinics.”

“Oral delivery of a taxane or microtubule-or tubulin-inhibitor mechanism of action would be a significant addition to our therapeutic armamentarium,” Shore added.

Although microtubule-targeting agents (MTAs), including taxanes and vinca alkaloids, are effective and widely used for treating a variety of cancers, resistance and toxicity can limit their clinical efficacy. In prostate cancer, resistance also builds up in patients who receive AR-targeting therapies. Approximately 15% to 25% of men do not respond to AR inhibitors and 75% to 85% progress within 9 to 15 months.³

Furthermore, as AR-targeting agents such as enzalutamide, darolutamide (Nubeqa), apalutamide (Erleada), and abiraterone are approved for earlier lines of treatment, patients with metastatic disease who progress on these agents need new options, according to Philip W. Kantoff, MD, chair of the Department of Medicine and George J. Bosl Chair at Memorial Sloan Kettering Cancer Center in New York, New York.

According to Kantoff, a 2014 Giants of Cancer Care® award winner in the genitourinary cancer category, novel therapies such as VERU-111 may allow patients to overcome acquired resistance to AR inhibitors. “Androgen-blocking agents are either introduced in the context of metastatic hormone-sensitive prostate cancer, nonmetastatic CRPC, or mCRPC,” he said in an interview with OncologyLive⁶. “It is leaving a void where we don’t have many drugs right now, so there is still a need for new therapies in mCRPC.”

FUTURE DIRECTIONS

The phase 2 portion of the study reported at ESMO 2020 is fully enrolled with 40 patients, Veru announced in September.⁴ The open label, single-arm trial will evaluate VERU-111 for efficacy and safety in patients who have become resistant to at least 1 AR-targeting therapy but who have not received intravenous (IV) chemotherapy in the metastatic setting. The key efficacy end point of the phase 2 portion is radiographic imaging of progression-free survival (rPFS).

Looking ahead, Veru is making plans for a phase 3 trial that would enroll 250 men with mCRPC who have rising PSA levels and tumor progression while receiving AR-targeting therapy. Participants would be randomized to receive either VERU-111 continuously at 63 mg daily or standard therapy with either abiraterone or enzalutamide, depending upon their prior treatment. The primary end point would be rPFS, with secondary end points of overall survival, time to IV chemotherapy, pain progression, and PSA responses.³

VERU-111 also has demonstrated antitumor activity in preclinical models of other tumor types, including taxane-resistant triple-negative breast cancer and lung cancer, pancreatic cancer, and melanoma.⁵ Additionally, the agent is currently undergoing testing as a potential treatment for coronavirus disease 2019 (COVID-19) in a phase 2 trial (NCT04388826). Investigators are seeking to randomize 40 patients with COVID-19 who are at high risk for acute respiratory distress syndrome to either 18 mg of VERU-111 or placebo. The primary efficacy end point for the 62-day study is the proportion of patients alive and without respiratory failure at day 29.

REFERENCES


MORE ON OncLive.com

Kantoff Puts VERU-111 Into Context

Philip W. Kantoff, MD, discusses the mechanism of action of VERU-111 and the rationale for investigating the therapy in patients with metastatic castration-resistant prostate cancer. He also puts the development of the therapy into the context of androgen receptor–targeting strategies in prostate cancer.

Kantoff, a 2014 Giants of Cancer Care® award winner, is chair of the Department of Medicine and George J. Bosl Chair at Memorial Sloan Kettering Cancer Center in New York, New York.

View Video: https://bit.ly/3fVXzRX

Early Data Show PSA Declines

Mark C. Markowski, MD, says VERU-111 monotherapy resulted in prostate-specific antigen (PSA) declines in 6 of 10 men treated with the recommended dose, according to findings from a phase 1b/2 study. Markowski reported the results during the European Society for Medical Oncology (ESMO) Virtual Congress 2020 in September.

Markowski, the lead study author, is an assistant professor of oncology at The Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland.

In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:

**29%**

reduction in risk of PFS event*

(HR: 0.71; 95% CI: 0.54, 0.93; P = 0.011): median PFS 48.2 vs 20.8 months

for A+CHP and CHOP, respectively; primary endpoint

*PFS was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease.

**Indication**

ADCETRIS® (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

**Important Safety Information**

**BOXED WARNING**

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

**Contraindication**

ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

**Warnings and Precautions**

- **Peripheral neuropathy (PN)**: ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
**ECHOLEN-2 trial design:** A multicenter, phase 3, randomized, double-blind, double-dummy, actively controlled trial in 452 patients with sALCL and other CD30-expressing PTCL. Patients were randomized 1:1 to A+CHP (n = 226) or CHOP (n = 226), and received treatment every 3 weeks for 6 to 8 cycles at investigator’s discretion. Primary endpoint was PFS per IRC, defined as progression, death from any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease. Overall survival was a key secondary endpoint.2,3

**Most common adverse reactions (≥20%) in combination with CHP**

Anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.2

A+CHP = ADCETRIS + cyclophosphamide, doxorubicin, prednisone; ALCL = anaplastic large cell lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHP = cyclophosphamide, doxorubicin, prednisone; CI = confidence interval; HR = hazard ratio; IRC = independent review facility; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma.

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**reduction in risk of death**

| HR = 0.66 | 95% CI: 0.46, 0.95 | P = 0.024 |

†Median overall survival follow-up of 42.1 months with A+CHP and CHOP; median overall survival not reached in either treatment arm.3

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Please see additional Important Safety Information and Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages. Full Prescribing Information available at adcetrispro.com
Important Safety Information, cont’d

- Anaphylaxis and infusion reactions: Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS® (brentuximab vedotin). Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

- Hematologic toxicities: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma or previously untreated PTCL.
  Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

- Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.

- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor and high tumor burden.

- Increased toxicity in the presence of severe renal impairment: The frequency of Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.

- Increased toxicity in the presence of moderate or severe hepatic impairment: The frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.

- Hepatotoxicity: Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatoxic injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- PML: Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

- Pulmonary toxicity: Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

- Serious dermatologic reactions: Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- Gastrointestinal (GI) complications: Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

- Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Most Common (≥20% in any study)
Adverse Reactions
Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

Drug Interactions
Concomitant use of strong CYP3A4 inhibitors or inducers has the potential to affect the exposure to monomethyl auristatin E (MMAE).

Use in Specific Populations
Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.
Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages and full Prescribing Information at adcetrispro.com


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.
WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
JC virus infection resulting in PML and death can occur in patients receiving ADECTRIS.

1 INDICATIONS AND USAGE
ADECTRIS is a CD19-targeted antibody-drug conjugate indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (SALCL) or other CD19-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL, not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
For dosing instructions of combination agents administered with ADECTRIS, see the manufacturer’s prescribing information.
Administer ADECTRIS as a 30-minute intravenous infusion. The recommended dose is 1.8 mg/kg up to a maximum of 180 mg in combination with cyclophosphamide, doxorubicin, and prednisone (CHP), administered every 3 weeks with each cycle of chemotherapy for 6 to 8 doses. Reduce the dose to patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance [Ccr] <30 mL/min). The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

2.2 Recommended Prophylactic Medications
In patients with previously untreated PTCL who are treated with ADECTRIS + CHP, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification
Peripheral Neutropenia: For Grade 2 motor neurotoxicity, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 sensory neurotoxicity, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 motor neurotoxicity, discontinue dosing. For Grade 4 sensory or motor neurotoxicity, discontinue dosing. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.
Neutropenia: For Grade 3 or 4 neutropenia, administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

4 CONTRAINDICATIONS
ADECTRIS is contraindicated in concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

5 WARNINGS AND PRECAUTIONS
5.1 Peripheral Neutropenia
ADECTRIS treatment causes a peripheral neutropenia that is predominantly sensory. Cases of peripheral motor neutropathy have also been reported. ADECTRIS-induced peripheral neurotoxicity is cumulative.
In ECHEN-2 (Study 6), 52% of patients treated with ADECTRIS + CHP experienced new or worsening peripheral neurotoxicity of any grade by maximum grade 34% Grade 2, 32% Grade 1, 1% Grade 0. The peripheral sensory nervous system showed predominantly sensory (84% sensory, 16% motor) and had a median onset time of 2 months (range <1-9). At last evaluation, 90% had complete resolution of neurotoxicity. 12% had partial improvement, and 8% had no improvement. The median time to resolution or improvement overall was 4 months (range, 4-96). Of patients with residual neuropathy at their last evaluation, the neuropathy was Grade 1 in 72%, Grade 2 in 25%, and Grade 3 in 3%.
Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADECTRIS.

5.2 Anaphylaxis and Infusion Reactions
Infusion-related reactions, including anaphylaxis, have occurred with ADECTRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADECTRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities
Fetal and serious cases of febrile neutropenia have been reported with ADECTRIS. Prolonged (>1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADECTRIS.
Start primary prophylaxis with G-CSF beginning with Cycle 1 for patients who receive ADECTRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma (CHL) or previously untreated PTCL.
Monitor complete blood counts prior to each dose of ADECTRIS. Monitor more frequently for patients with Grade 3 or 4 neutropenia. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADECTRIS doses.

5.4 Serious Infections and Opportunistic Infections
Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADECTRIS. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome
Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment
The frequency of Grade 3 or 4 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MAAE exposure, Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADECTRIS in patients with severe renal impairment (Ccr <30 mL/min).

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment
The frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with no hepatic dysfunction. Avoid the use of ADECTRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

5.8 Hepatotoxicity
Focal and serious cases of hepatoxicty have been reported in patients receiving ADECTRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADECTRIS or after ADECTRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADECTRIS.

5.9 Progressive Multifocal Leukoencephalopathy
Focal cases of JC virus infection resulting in PML have been reported in ADECTRIS-treated patients. Use of ADECTRIS is associated with an increased risk of PML in patients with HIV. Evaluate patients for signs of progression of multifocal leukoencephalopathy at regular intervals. In patients with multifocal leukoencephalopathy, ADECTRIS is associated with an increased risk of PML. Discontinue ADECTRIS if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity
Focal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADECTRIS dosage during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions
Focal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADECTRIS. If SJS or TEN occurs, discontinue ADECTRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications
Focal and serious events of acute pancreatitis have been reported. Focal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, necrotizing colitis, and dehiscence of GI tract. In patients with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, ADECTRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADECTRIS in pregnant women. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks.
Advise females of reproductive potential to avoid pregnancy during ADECTRIS treatment and for at least 6 months after the final dose of ADECTRIS. Advise a pregnant woman of the potential risk to the fetus.

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 (≥20%) in combination with CHOP were anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

**Previously Untreated sALCL or Other CD30-Expressing PTCL (Study 6, ECHOLEON-2)**

ADCETRIS in combination with CHOP was evaluated in patients with previously untreated, CD30-expressing PTCL, in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. Patients were randomized to receive ADCETRIS + CHOP or CHOP for 6 to 8, 21-day cycles. ADCETRIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously every 30 minutes, approximately 1 hour after completion of CHOP. The trial required hepatic transaminase ≤3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy.

A total of 449 patients were treated (223 with ADCETRIS + CHOP, 226 with CHOP), with 6 cycles planned in 81%. In the ADCETRIS + CHOP arm, 70% of patients received 6 cycles, and 18% received 8 cycles. Primary prophylaxis with G-CSF was administered to 94% of ADCETRIS + CHOP-treated patients and 27% of CHOP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the CHOP arm and in 4% of patients in the ADCETRIS + CHOP arm, most often from infection. Serious adverse reactions were reported in 38% of ADCETRIS + CHOP-treated patients and 35% of CHOP-treated patients. Serious adverse reactions occurring in ≥2% of ADCETRIS + CHOP-treated patients included febrile neutropenia (14%), pneumonia (9%), pyrexia (9%), and sepsis (9%).

The most common adverse reactions observed ≥2% more in recipients of ADCETRIS + CHOP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and headache (see Table 6, ECHOLEON-2). Other common (≥1%) adverse reactions observed ≥2% more with ADCETRIS + CHOP were febrile neutropenia, abdominal pain, decreased appetite, dyspnea, edema, cough, dizziness, hypokalemia, decreased weight, and myalgia.

In recipients of ADCETRIS + CHOP, the adverse reactions led to dose delays of ADCETRIS in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCETRIS with or without other components in 7% (most often from peripheral neuropathy and infection).

### Table 7: Adverse Reactions Reported in ≥10% of ADCETRIS + CHOP-Treated Patients with Previously Untreated, CD30-Expressing PTCL (Study 6, ECHOLEON-2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCETRIS + CHOP</th>
<th>CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia†</td>
<td>66</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia†</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Lymphopenia†</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Mucositis</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>52</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

### Table 7: Adverse Reactions, cont’d

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCETRIS + CHOP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

*Derived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and end of treatment.

The table includes a combination of grouped and ungrouped terms. CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone. COP = cyclophosphamide, vincristine, dactinomy, and prednisone. Events were graded using the NCICTAE Version 4.03.

### Additional Important Adverse Reactions

**Infusion Reactions**

In a study of ADCETRIS in combination with CHOP (Study 6, ECHOLEON-2), infusion-related reactions were reported in 10 patients (4%) in the ADCETRIS + CHOP-treated arm: 21% patients with events that were Grade 3 or higher events, and 8% (4%) patients with events that were less than Grade 3.

**Pulmonary Toxicity**

In a trial in patients with CHL, that studied ADCETRIS with bortezomib as part of a combination regimen, the rate of non-focal pulmonary toxicity was higher than the historical incidence reported with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), Patients typically reported cough and dyspnea, interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bortezomib is contraindicated.

In a study of ADCETRIS in combination with CHOP (Study 6, ECHOLEON-2), non-infectious pulmonary toxicity events were reported in 5 patients (2%) in the ADCETRIS + CHOP arm, all events were pneumonitis.

### 6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Blood and lymphatic system disorders: febrile neutropenia. Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes). Hepatobiliary disorders: hepatotoxicity. Infections: PMV, serious infections and opportunistic infections. Metabolism and nutrition disorders: hyperglycemia. Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes). Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, including fatal outcomes.

### 6.3 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 ADCETRIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (62%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MV801, which may increase the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug’s mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicity, including increased fetal resorption, decreased fetal body weight, decreased fetal skin thickness, and increased fetal abnormalities (i.e., umbilical hernias and multicystic hindbrains). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary
There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from ADCETRIS, including cytophenias and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug’s mechanism of action.

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

Contraception
Females
Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

Males
ADCETRIS may damage spermatogonia and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility
Males
Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

8.4 Pediatric Use

Safety and effectiveness of ADCETRIS have not been established in pediatric patients.

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHOLEN-2), 91% of ADCETRIS + CHP-treated patients were age 65 or older. Among older patients, 74% had adverse reactions ≥Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 82% had adverse reactions ≥Grade 3 and 93% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 28% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment
Avoid the use of ADCETRIS in patients with severe renal impairment (CrCl <30 mL/min). No dosage adjustment is required for mild (CrCl >50–80 mL/min) or moderate (CrCl 30–50 mL/min) renal impairment.

8.7 Hepatic Impairment
Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment.

10 OVERDOSAGE
There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

17 PATIENT COUNSELING INFORMATION

Peripheral Neuropathy: Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbing or tingling of the hands or feet or any muscle weakness.

Fever/Neutropenia: Advise patients to contact their health care provider if they have a fever of 100.3°F or greater or other evidence of potential infection such as chills, cough, or pain on urination during the week of infusion.

Infusion Reactions: Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion.

Hepatotoxicity: Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Progressive Multifocal Leukoencephalopathy: Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms: changes in mood or usual behavior, confusion, thinking problems, loss of memory, changes in vision, speech, or walking, decreased strength or weakness on one side of the body.

Pulmonary Toxicity: Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath.

Acute Pancreatitis: Advise patients to contact their health care provider if they develop severe abdominal pain.

Gastrointestinal Complications: Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea.

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcertris.com

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All rights reserved. REF-106S
Novel Mechanism of Action and Tolerability Make Telaglenastat a Promising Player in RCC

by ERICA DINAPOLI

TELAGLENASTAT (CB-839), AN ORAL inhibitor of human glutaminase, has been evaluated in combination with several agents across tumor types to determine whether its novel mechanism of action would improve clinical responses. Specifically, data have shown that the agent in combination with everolimus (Afinitor) in patients with renal cell carcinoma (RCC) was well tolerated and demonstrated a response in heavily pretreated patients, according to Chung-Han Lee, MD, PhD.

Results from the phase 2 ENTRATA trial (NCT03163667) presented during the European Society for Medical Oncology (ESMO) Congress 2019 showed that the addition of telaglenastat to everolimus extended progression-free survival (PFS) compared with everolimus mono-therapy in patients with advanced or metastatic RCC who received at least 2 prior therapies, including at least 1 VEGFR-targeting tyrosine kinase inhibitor. The median PFS with telaglenastat/everolimus was 3.8 months versus 1.9 months with single-agent everolimus (HR, 0.64; 95% CI, 0.34-1.20; 1-sided \( P = .079 \)). Further, 56.5% of patients treated with the combination \( (n = 46) \) had stable disease compared with 47.8% treated with everolimus alone \( (n = 23) \). This trial provided proof of principle to examine the agent further, Lee said.

“For the longest time, the majority of agents that we had for RCC were either angiogenesis inhibitors, mTOR inhibitors, or immune checkpoint inhibitors,” Lee said. “However, telaglenastat truly represents an entirely new class of medications…now being studied. [Because of] its new mechanism of action—and the fact that it’s well tolerated—it is a very exciting addition to the paradigm.”

Telaglenastat is under exploration in combination with cabozantinib (Cabometyx) compared with cabozantinib alone in patients with advanced or metastatic RCC with a clear cell component who had received more than 2 previous therapies in the phase 2 CANTATA trial (NCT03428217), Lee added. In an interview with OncologyLive®, Lee, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, discussed the promise of telaglenastat in RCC and the research efforts examining the agent in different combinations.

Please describe telaglenastat’s novel mechanism of action.

Telaglenastat, also known as CB-389, is a glutaminase inhibitor that inhibits the conversion of glutamine into glutamate. Generally, when we think about cancer, 2 main energy sources are critical: the glucose pathway and the glutamine pathway.

Part of the Warburg effect is the conversion and over reliance on glycolysis, or the utilization of glucose to generate energy. However, in order to populate different aspects of the tricarboxylic acid (TCA) cycle, many different malignancies rely on glutamine as a source of carbon. Telaglenastat essentially blocks that utilization.

How does the agent affect tumor metabolism in this disease?

RCC has been studied extensively and is thought to be a metabolic malignancy, meaning many different metabolic alterations are important to pathogenesis. Several preclinical studies have demonstrated that almost all the molecules within the TCA cycle rely on glutamine in order to produce those numbers. Also, the molecules from glutamine are important for fatty acid synthesis.

Telaglenastat blocks the ability of the cells to utilize glutamine. This is why multiple clinical studies [were conducted] to see whether altering that metabolism can be important for treatment as a novel mechanism.

What research has been conducted with telaglenastat?

Telaglenastat has been studied in RCC in multiple formats. The agent has been evaluated, not only in combination with an immune checkpoint inhibitor, but [it was] also studied in ENTRATA in combination with everolimus, which is an mTOR-targeted agent.

During the 2019 ESMO Congress, we presented [data on] the combination of telaglenastat and everolimus versus everolimus alone. In the study, patients were randomized 2:1 to receive either the combination or everolimus monotherapy. We wanted to see whether using this novel agent and targeting a new mechanism of action would improve the clinical responses seen with metabolic inhibitors, such as everolimus.

[Results showed] an improvement in PFS in this small, proof-of-principle study. The numbers did not yet meet their statistical significance; however, they did meet [the primary end point] based on the power setting ratings that were established for the clinical trial design. We must think of this as a proof of principle, showing that there is activity using this new mechanism of action.

What are the next steps for this agent?

Within RCC, perhaps one of the most important studies with telaglenastat, right now, is a randomized phase [2] study of the combination of telaglenastat plus cabozantinib versus cabozantinib alone [CANTATA]. This is a very large study consisting of about 400 patients, which will demonstrate the efficacy of the compound. This will also give us more information regarding not only the safety and tolerability but also the efficacy.

REFERENCE

Emerging Therapies May Offer Fresh Options for TP53-Mutated MDS

by JASON HARRIS

TWO NOVEL TREATMENT OPTIONS may shake up the landscape for treating patients with myelodysplasia syndrome (MDS). Eprenetapopt (APR-246) and magrolimab have the potential to be game changers for patients with high-risk MDS, according to Rami Komrokji, MD. Both agents received breakthrough therapy designations from the FDA in 2020 and have demonstrated efficacy in patients with TP53 mutations.

“It’s exciting that we finally have so many options to offer our patients,” Komrokji said in an interview with OncologyLive®. “It [has been] more than a decade where we did not get new drugs approved after azacitidine and decitabine.” Komrokji is a professor of medicine and oncologic sciences at the College of Medicine of the University of South Florida, section head of leukemia and MDS, and vice chair of the Moffitt Cancer Center in Tampa, Florida.

“The most promising front-runners [include] APR-246 and, hopefully down the road, the oral formulation of that and magrolimab,” he said.

Komrokji said that eprenetapopt modulates the mutated TP53, thereby restoring wide function to the gene. Furthermore, the agent has showed an additive effect with azacitidine (Vidaza) in prior trials.

A French phase 2 study (NCT03588078) conducted by Groupe Francophone des Myélodysplasies enrolled patients with TP53-mutated MDS or acute myeloid leukemia (AML) who were treated with eprenetapopt plus azacitidine. Participants received 4500 mg per day of intravenous eprenetapopt on days 1 to 4 and 75 mg/m² of subcutaneous azacitidine on days 4 to 10 every 28 days for 6 cycles. Those who responded to the combination continued on therapy until relapse.

In findings presented at the 2020 European Hematology Association Congress, response rate in the intention-to-treat (ITT) population was 62% among patients with MDS (n = 34), including a 47% complete remission (CR) rate; 64% among those with AML with 20% to 30% blasts (n = 11), including a 27% CR rate; and 29% for those with AML with greater than 30% blasts (n = 7), with no CRs.1 The median OS was 12.1 months (95% CI, 8.9-15.3) for both the entire group (n = 52) and for the MDS cohort after a median follow-up of 9.7 months. For patients who remained on treatment for 3 or more cycles, the median OS was higher at 13.7 months (95% CI, 11.7-15.7) versus 2.8 months (95% CI, 1.2-4.4) for patients who were on treatment for fewer than 3 cycles (P < .0001).

Enrollment for a randomized, controlled phase 3 trial (NCT03745716) evaluating eprenetapopt/azacitidine versus azacitidine alone as frontline therapy in intermediate-, high-, and very high-risk patients with TP53-mutant MDS finished in June. Investigators plan to have topline results by the end of this year.

“If those data are positive, I think that will lead to approval of the drug to be available for patients with a TP53 mutation,” Komrokji said.

MAGROLIMAB OUTPERFORMS AZACITIDINE

Magrolimab is a first-in-class, investigational anti-CD47 monoclonal antibody for the treatment of newly diagnosed MDS. Data from an ongoing phase 1b trial (NCT03248479) evaluating magrolimab in combination with azacitidine in treatment-naïve patients with high- and very high-risk MDS showed that the regimen was well tolerated and effective in this patient population.

A total of 91% (30 of 33) of evaluable patients had an objective response to the combination; 42% had a CR, and 24% experienced a CR in the bone marrow. The median time to initial response was reported to be 1.9 months, which is faster than what is expected with azacitidine alone.2 Komrokji noted that azacitidine monotherapy typically induces CR rates of approximately 20%.

Additionally, those who responded to the treatment experienced deeper responses over time; the CR rate in those with 6 months of follow-up or longer was 56%. Investigators observed cytogenetic CRs in 35% of patients evaluable for response. Moreover, 22% of patients with CR or CR with incomplete hematologic recovery in the bone marrow also had minimal residual disease negativity per multiparameter flow cytometry.

Based on these results, investigators will assess the magrolimab/azacitidine combination versus azacitidine alone for patients with intermediate- to very high-risk untreated MDS in the phase 3 ENHANCE trial (NCT04313881).

Komrokji added that patients with TP53-mutated AML up front also had high responses with the magrolimab and that the monoclonal antibody appeared to be agnostic to all somatic mutations.

“If [the phase 3 data are] positive, it will lead to an approval [of magrolimab],” he said. “[Magrolimab] is also is going into a randomized, phase 3 trial in patients with TP53-mutant AML compared with azacitidine because, even with azacitidine/venetoclax [Venclexta] becoming the standard of care for patients with AML, the group that did not do well were [those who had a] TP53 mutation—magrolimab had shown promising activity even among that group. I think the drug looks very promising and is well tolerated. Hopefully that will translate to another option for our patients.”

“I think the next step down the road will be integrating all these promising drugs,” Komrokji said. “You have venetoclax, you have APR-246 and magrolimab. Maybe we’ll be talking about the combination of those drugs, as well.”

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

MONJUVI®
tafasitamab-cxix | 200mg
for injection, for intravenous use

FDA-approved monoclonal antibody in combination with lenalidomide for adult patients with R/R DLBCL who have received at least one prior therapy

Learn more at MonjuviHCP.com

INDICATIONS & USAGE
MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

IMPORTANT SAFETY INFORMATION
Contraindications
None.

Warnings and Precautions
Infusion-Related Reactions
MONJUVI can cause infusion-related reactions (IRRs). In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication. Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor complete blood counts (CBC) prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony stimulating factor (G-CSF) administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose. In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Embryo-Fetal Toxicity
Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of potential risk to a fetus. Advise women of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women, because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Adverse Reactions
The most common adverse reactions (≥20%) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to MORPHOSYS US INC. at (844) 667-1992.

Please see the Brief Summary of Prescribing Information on the following pages.
BEST OVERALL RESPONSE RATE IN PATIENTS WITH R/R DLBCL (N=71)†

L-MIND STUDY DESIGN
- L-MIND was an open-label, multicenter, single-arm study that evaluated efficacy and safety of MONJUVI in combination with lenalidomide followed by MONJUVI monotherapy in adult patients with R/R DLBCL after 1 to 3 prior systemic DLBCL therapies, including a CD20-containing therapy. The median number of prior therapies was 2.
- Enrolled patients at the time of the trial were not eligible for or refused ASCT.
- Efficacy was established in 71 patients with DLBCL (confirmed by central laboratory) based on best ORR (defined as the proportion of complete and partial responders) and DoR.

DURATION OF RESPONSE IN PATIENTS WITH R/R DLBCL (N=71)†

Median DoR: 21.7 months (range: 0, 24)†

SAFETY PROFILE†
- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in other clinical trials of another drug and may not reflect the rates observed in practice.
- Serious adverse reactions occurred in 52% of patients who received MONJUVI.
  - Serious adverse reactions in ≥6% of patients included infections (26%) including pneumonia (7%), and febrile neutropenia (6%).
  - Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%), and sudden death (1.2%).
- Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%.
  - The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).
- Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%.
  - The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

For more details on Adverse Reactions, refer to the full Prescribing Information.

INDICATIONS AND USAGE
MONJUVI, in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
MONJUVI can cause infusion-related reactions. In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication.

Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor CBC prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony stimulating factor administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections
Fatal and/or serious infections including opportunistic infections have occurred in patients during treatment with MONJUVI and following the last dose.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Embryo-Fetal Toxicity
Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women, because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
The safety of MONJUVI was evaluated in L-MIND. Patients (n=81) received MONJUVI 12 mg/kg intravenously in combination with lenalidomide for maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Among patients who received MONJUVI, 57% were exposed for 6 months or longer, 42% were exposed for greater than one year, and 24% were exposed for greater than two years. Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥6% of patients included infections (26%) including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections and infestations (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions (≥ 20%) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MONJUVI (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>38</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection†</td>
<td>24</td>
</tr>
<tr>
<td>Urinary tract infection†</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>19</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15</td>
</tr>
</tbody>
</table>

* Fatigue includes asthenia and fatigue
† Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection

Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal

Table 3 summarizes the adverse reactions in L-MIND.

Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:

- Blood and lymphatic system disorders: lymphopenia (6%)
- General disorders and administration site conditions: infusion-related reaction (6%)
- Infections: sepsis (4.9%)
- Investigations: weight decreased (4.9%)
- Musculoskeletal and connective tissue disorders: arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- Neoplasms benign, malignant and unspecified: basal cell carcinoma (1.2%)
- Nervous system disorders: headache (9%), paresthesia (7%), dysequisia (6%)
- Respiratory, thoracic and mediastinal disorders: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- Skin and subcutaneous tissue disorders: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)
MONJUVI® (tafasitamab-cxix)

Table 4 summarizes the laboratory abnormalities in L-MIND.

Table 4: Select Laboratory Abnormalities (>20%) Worsening from Baseline in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase increased</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Aspartate Aminotransferase increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated Partial Thromboplastin Time increased</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

1 The denominator used to calculate the rate was 74 based on the number of patients with a baseline value and at least one post-treatment value.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assays. 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 tafasitamab products may be misleading.

Overall, no treatment-emergent or treatment-booster anti-tafasitamab antibodies were observed. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety profile of tafasitamab-cxix were observed in 2.5% of 81 patients with relapsed or refractory DLBCL with pre-existing anti-tafasitamab antibodies in L-MIND.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. There are no available data on MONJUVI use in pregnant women to evaluate for a drug-associated risk. Animal reproductive toxicity studies have not been conducted with tafasitamab-cxix.

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.

MONJUVI is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide prescribing information for additional information. Lenalidomide is only available through a REMS program.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G (IgG) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, MONJUVI may cause depletion of fetal CD19 positive immune cells. Defer administering live vaccines to neonates and infants exposed to tafasitamab-cxix in utero until a hematology evaluation is completed.

Data

Animal Data

Animal reproductive studies have not been conducted with tafasitamab-cxix. Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

Lactation

Risk Summary

There are no data on the presence of tafasitamab-cxix in human milk or the effects on the breastfed child or milk production. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to MONJUVI are unknown. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose. Refer to lenalidomide prescribing information for additional information.

Females and Males of Reproductive Potential

MONJUVI can cause fetal B-cell depletion when administered to a pregnant woman.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose. Additionally, refer to the lenalidomide prescribing information for additional recommendations for contraception.

Males

Refer to the lenalidomide prescribing information for recommendations.

Pediatric Use

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

Geriatric Use

Among 81 patients who received MONJUVI and lenalidomide in L-MIND, 72% were 65 years and older, while 38% were 75 years and older. Clinical studies of MONJUVI did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs compared to that of younger subjects. Patients 65 years and older had more serious adverse reactions (57%) than younger patients (39%).

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full Prescribing Information.

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**DON S. DIZON, MD,** dances in TikTok videos. On Twitter, he does heartfelt voiceovers about caring for patients with cancer as he puts on a matching tie and face mask, which he makes himself. At other times, as he gets dressed, a voiceover of Maya Angelou reads 1 of her poems.

Through such touching moments, Dizon, who is a professor of Medicine at Brown University, the director of Breast and Pelvic Malignancies at Lifespan Cancer Institute and the director of medical oncology at Rhode Island Hospital in Providence, has been able to break barriers of cancer communication.

“The general public generally doesn’t pay attention to cancer-related content, until they are affected by it personally or with a loved one,” he said in an interview with OncologyLive®. “There has always been this question of how to increase cancer awareness in the general public. That sparked this idea of using these videos on TiKTok. People are looking for voices they can reliably count on.”

There is no doubt that the use of social media has exploded in the past 15 years. In 2005, just 5% of American adults used at least 1 social media platform. By 2011, that share had risen to half of all Americans, and in 2019, 72% of the public used some form of social media, according to results of surveys conducted by the Pew Research Center.¹

For patients with cancer, social media can provide support and engagement. Most platforms, including Facebook, Twitter, and YouTube, have cancer-specific content. Patients with cancer appear to be most active on Twitter, with 26.5% of conversations around cancer happening on this platform, according to an analysis conducted in 2019 by social media analytics company Synthesio.²

Women aged 18 to 34 years are the most vocal participants online, according to Synthesio. About one-third of these conversations (33.2%) revolve around diagnosis. Support is the next most-talked-about topic (27.6%).

Social media is a great avenue for patients, patient advocates, residents, and fellows to get access in real time to information, said Tatiana M. Prowell, MD, associate professor of oncology at The Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland.

“‘This is a big reason why I am on Twitter: This is a democratized access to knowledge,’” she said at the 38th Annual Chemotherapy Foundation Symposium® (CFS®) virtual conference in November. “I like the ability to interpret science and medicine for a broader audience.”

Prowell, who has more than 26,000 followers on Twitter, said social media provides an opportunity to provide accurate public health information and to counteract misinformation, especially regarding coronavirus disease 2019 (COVID-19). “We have to be in this space to accurately interpret information,” she said. “We might be oncologists but we are also health care workers, which means we have a huge role in getting out accurate information about the pandemic.”

For Lecia Sequist, MD, MPH, her use of Twitter has evolved over time. As director of the Center for Innovation in Early Cancer Detection at Massachusetts General Hospital in Boston, she thought she would use this platform for professional purposes, posting, and keeping updated about lung cancer, her specialty.

“Over time, I’ve realized how powerful #MedTwitter can be,” she said in an interview. “As I’ve learned more about the platform and grown more comfortable, I have started tweeting about a broader range of issues adjacent to lung cancer, including health care policy and health-care topics that could be categorized as political such as gun control and equity.”

She said tweets that especially resonate with her followers are about the stigma faced by patients who receive a diagnosis of lung cancer. “It is a good way to get a message out,” she said. “But it’s also a platform to have a conversation, either with other experts or with patient advocates.”

Dizon, who has 11,000 followers on Twitter, said he responds to everyone who comments on his posts. “I believe in bidirectionality,” he said.
USING SOCIAL MEDIA TO COMMUNICATE WITH COLLEAGUES

Physicians’ use of social media appears to be increasing, and Twitter is a favored platform, although it is difficult to estimate how many oncologists are active users of social media. Findings from a 2016 survey of Canadian oncology physicians and oncology trainees showed that physicians aged 25 to 34 years were more likely than those in other age groups to post on social media platforms. Barriers to social media use cited by the respondents included not having the time, preferring more traditional ways of accessing medical news, and concerns about privacy.

More recently, a presentation at the 2020 American Society of Clinical Oncology Virtual Scientific Program in May looked at Twitter use among 442 trainees in hematology-oncology. The survey found that 46% use Twitter for professional activities, including educating, disseminating information, and networking.

S. Vincent Rajkumar, MD, a 2019 Giants of Cancer Care® award winner in the myeloma category, was an early adopter of Twitter. He signed up in 2009 and currently has more than 31,000 followers.

“I sensed early on that Twitter would be the perfect forum for academic discussion for a larger group of people, many of whom you may not know,” said Rajkumar, who is the Edward W. and Betty Knight Scripps Professor of Medicine and a clinical investigator at Mayo Clinic in Rochester, Minnesota.

But Rajkumar said the number of followers is not as important as the quality of the information dispensed and whether it is articulated in a clear way. “Opinions on controversial topics get a lot of attention, and tweets that pose questions also get a lot of engagement with likes and followers,” he said. “People will follow you if they find you authentic and credible. That takes time to establish.”

Connecting with peers is another reason to be active on Twitter, he said. “It’s a good medium for learning and for the dissemination of information. I do see Twitter as important for academics, just as papers, publications, and lectures, and can help people advance in their careers.

People who are not on Twitter may be left behind,” he said.

Cathy Eng, MD, began using Twitter to make sure her patients had accurate information but also has found a large audience among peers. She has more than 7000 followers on Twitter.

“Social media can add to your career with regard to increased recognition by peers, by patients, and patient advocates,” said Eng, who is the David H. Johnson Chair in Surgical and Medical Oncology, codirector of Gastrointestinal Oncology, coleader of the Gastrointestinal Cancer Research Program, and director of the Young Adult Cancers Program at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee.

“It gives you a voice,” she said. “It is a good way to showcase some of the work you and your colleagues are doing. I’ve met a lot of people [through Twitter] I probably wouldn’t have met. I also meet a lot of individuals who thank me for posting from a meeting they couldn’t attend. That really helps update the knowledge base of community physicians as well.”

Sequist, who has more than 6600 followers on Twitter, encourages those she mentors to participate in social media after investigating the platforms they would be comfortable using. “It is a nice way to get your opinion out there, especially when you are starting out. Traditionally, before there were social media platforms, people starting out in academic medicine had to wait several years before having the opportunity to lend their opinions to the conversation. Twitter is a great platform for junior scientists to share their opinions without being interrupted and in a way that works for them,” she said.

Social media platforms also provide an avenue to discuss new research and ideas about cases, similar to an informal tumor board, Prowell said in her CFS® presentation. “It gives you a chance to build relationships and provides an opportunity to find colleagues to collaborate with. This is critical during this pandemic when we are all social distancing,” she said.

One recent study found social media is an effective tool to increase article reach and knowledge translation. Investigators looked at Altmetric Attention Scores, which assess articles’ mentions in blogs, mainstream media, and social media, and how they correlated with citations.

Specifically, investigators reviewed 50 articles with the highest Altmetric scores published in The Annals of Thoracic Surgery in 2013, 2015, and 2017. Over time, Altmetric scores increased significantly, from 11.9 in 2013 to 24.8 in 2015 and 75.3 in 2017 ($P < .001$).

FIGURE. Tips for Tweeting From Oncology Influencers

- **Be authentic.**
- **When tweeting from meetings, focus on important findings that are not being covered by others.**
- **Take the time to understand Twitter or other platforms before engaging.**
- **Uplift others by retweeting and liking their tweets.**
- **Follow key people in your field.**
- **Engage people in conversation.**
- **Address hot topics or new findings from research.**
- **Include the hashtag of your institution to generate traffic.**
The percentage of authors who turned to Twitter to discuss scholarly work increased from 10% in 2013 to 20% in 2015 and 42% in 2017 ($P < .001$). On multivariate analysis, tweets (OR, 1.27; 95% CI, 1.01-1.61; $P = .044$) and mentions by news outlets (OR, 30.49; 95% CI, 4.04-230.16; $P = .001$) were predictive of high Altmetric scores.

Social media also can be a valuable tool for keeping up with medical knowledge, Prowell said.

“The doubling time of medical knowledge in 1950, just by the proliferation of textbooks and news articles, was a half century,” she said. “By 1980, the doubling time was 7 years, and a decade ago it was 3.5 years, and now it is 0.2 years. It is not an exaggeration to say we just can’t keep up with medicine, and you can’t even keep with oncology. So how do we decide where to direct our attention or to ensure we aren’t missing something? I would argue social media is the best current approach.”

Prowell started using Twitter in 2017 during the San Antonio Breast Cancer Symposium. “I wanted to see what people were saying about the sessions I wasn’t able to attend. I also wanted to keep patient advocates and fellows I mentored who weren’t able to attend informed.”

**ADVICE FOR USING SOCIAL MEDIA**

Oncology influencers have developed strategies and best practices for using social media gleaned from experience (FIGURE). Since she began using Twitter, Prowell said, she has learned how to employ hashtags and bots to flag content that is of greatest interest to her. She recommends using a tool such as TweetDeck as a way to manage the information coming through.

When tweeting, Prowell said, it is important to use hashtags. “They are like the labels on a filing cabinet. This is what gets the tweet to where it needs to go for people who are interested on this topic. I would encourage people, despite the character limitations, to avoid medical abbreviations because when we use them that might result in confusion that you may not intend.”

Eng stressed that the institution hashtag also should always be included. “This will help to gain an active Twitter following and lets people know where you are from.”

Dizon said the biggest lesson he has learned through his experience is to be authentic and responsive. On a broader level, Dizon suggested being cautious about requests to use your “brand” to promote messaging.

“That is a dangerous thing to do. I’ve always said no to those things. On social media as a clinician, a researcher, and an academic, we can’t do.”

Dizon is a founder of The Collaboration for Outcomes using Social Media in Oncology, which aims to inform the cancer community about the potential value of cancer communication.

“We wanted to encourage participation and engagement but also provide guidance about how to do it thoughtfully,” he said. “For those who aren’t on social media, take the time to explore the channels. Every now and then, I’ll explore a new channel and I’ll see if it is something that works for me. I think that is a question people need to ask themselves: Does this work for me?”

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

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**Expert Recommends Reviewing Your Employee Handbook**

**by CAROL GIBBONS, BSN, RN, NHA**

**MANY HEALTH CARE BUSINESSES** have employee policy handbooks or handouts but fail to update them on a regular basis.

Here are some items to include:

1. **Social media**: Do you have a social media policy?
   
   You can prohibit the use of social media in the work area during business hours and on company computers.

2. **At-will employment**: If your state has an at-will employment law, you also should have a statement that the handbook cannot be considered a contract and that you have the right to make changes in an employee’s status whenever you feel necessary.

3. **Disciplinary procedures**: Do you have a long list of things employees might do that would result in disciplinary action? You may want to review that process and delete the list. Consider instead having a statement about honesty, ethics, respect, and the attributes you expect from employees.

4. **Harassment**: Do you have a policy that says harassment should be reported to an employee’s manager or supervisor? Keep in mind that the manager/supervisor could be the person harassing the employee. You might want to give the employee the option of reporting to any manager. They need a way to report that does not affect their job.

5. **Benefits**: Have you reviewed your company’s benefits to ensure they comply with federal and state laws?

6. **Leave and personal time off (PTO)**: Does your handbook explain specifically how these will be accrued? Whether you choose to offer vacation and sick leave or PTO, you need to document how they will be calculated and when the employee will be eligible for these benefits.

Carol Gibbons, BSN, RN, NHA, is a health care business consultant. Send your legal questions to medec@mjlifesciences.com.
PROOF Trial
Now Enrolling:

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

Take the Next Step

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:

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Pandemic Inspires New Outreach Program

by MITCHELL C. POSNER, MD

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IT HAPPENS TO ONCOLOGISTS all the time. A friend or acquaintance pulls you aside, seeking a little advice following a diagnosis of cancer. They hope for news of a great new treatment, but, fundamentally, they are seeking assurance that a care team is ready to guide a patient expertly, efficiently, and with empathy through the maze of therapeutic options.

As oncologists, we are here to help patients and their families as much as we can. That is why we went into cancer medicine. It is what we do every day.

Until the coronavirus disease 2019 (COVID-19) pandemic knocked on our doors. In March 2020, as we struggled to flatten the curve, care for seriously ill patients with COVID-19, and ensure the safety of everyone on our medical campus, the University of Chicago (UChicago) Medicine and other institutions were forced to cut back on surgeries and shutter clinics. Cancer screenings stopped. With the city under a stay-at-home order, patients were reluctant to see a doctor in person or come to the hospital.

But we did not sit still. Given the growing constriction on personal protective equipment, staff, and resources because of burgeoning COVID-19 hospitalizations, UChicago Medicine surgeons from all disciplines collaborated to develop a system to manage resources ethically and efficiently during the pandemic. Details of this prioritization scoring system, called Medically Necessary, Time-Sensitive (MeNTS) procedures, were published in August.

However, there was more to do within the cancer realm. We already had one example of the role telemedicine could play at our institution. UChicago Medicine’s Remote Second Opinion program debuted in April 2019. Although the program is multidisciplinary, approximately 50% of requests to use it have been for cancer consultations, and 60% have been to interact with international patients.

Additionally, our team developed a number of new approaches to pandemic cancer care that included scheduling virtual visits for our patients. Our focus soon centered on the need not only to provide continued medical access to current patients, but also to provide those who had received new diagnoses with perspective, information, and reassurance.

We wanted to address the concerns of these patients who now faced closed clinics and no clear path forward, such as a woman referred for a mammogram because she felt a lump, and who thinks, “It’s breast cancer for sure. What do I do now?”

The first thing many patients with a new diagnosis do is to call their family and close friends, creating a nest of anxiety. Those loved ones try to help with opinions and stories about what other people they know have gone through. Everyone goes online, reading things that have no context to the individual in question. Many say not to worry, but of course the patient does; their diagnosis is a life-changing event.

The idea was simple enough; the UChicago Medicine team encouraged these quarantined patients with cancer to call us. Within a short time, the idea evolved into a formal pilot program called the Express Expert Cancer Opinion (EECO). The program is for patients to connect with a UChicago Medicine cancer expert for 15 minutes via video or over the phone. Sessions are scheduled with a cancer expert in the field related to the diagnosis within 24 to 48 hours of the patient’s first call. Families can participate and the program is available at no cost to the patient.

During the sessions, clinicians try to provide a sense of calm to patients and convey the empathy we feel and hopefully relieve some of their anxiety.

Given that all we know is their diagnosis—no medical records or scans are required to participate—we aim to provide hope as well as a realistic, if generic, blueprint of what care could entail.

Although we can only speak in general terms, we can offer a lot of information during that time, providing a landscape of what lies ahead. Discussions can include information about workups that may be needed, possible treatments that may be offered, and clinical trials that are available. Answers to common queries about risk of death or life expectancy are not provided as we do not have all the relevant data, and that is never a casual conversation. But we do emphasize that it matters where they first receive care, and that it is best if they seek a treatment plan from a multidisciplinary team of cancer physicians who have experience with the latest advances and who have access to clinical trials. Typically, this includes many cancer centers.

Our experience suggests that this program is popular, sustainable, and humane. The EECO was launched on June 22, 2020, and 35 patients had an EECO session in the first 3 months, half of whom live outside the cancer center’s traditional service areas. Nevertheless, 80% of those who called the EECO line scheduled a visit to the University of Chicago Medicine Comprehensive Cancer Center as a new patient.

We do not think of EECO as marketing our services, but rather as an educational, public service approach to assisting patients with cancer during the COVID-19 pandemic. More than 40 of our cancer specialists are now participating, each of whom is volunteering their time. There has been so much support. We are reaching out to anyone who wants guidance, helping patients to navigate their cancer voyage.

EECO is something we can all do with a video link, a little time, and a good dose of compassion. The beauty lies in its simplicity.

REFERENCE
**Novel Strategy Gains Traction Against HRAS-Mutant Cancers**

by JANE DE LARTIGUE, PhD

**MORE THAN A QUARTER OF A** million new cases of RAS-mutant cancer are diagnosed each year in the United States,\(^1\) making the pathway a high-priority target for cancer therapy. Despite decades of research and drug development, however, the therapeutic utility of targeting RAS is limited to ruling out treatment with certain drugs in patients without RAS mutations.\(^2,3\)

The reasons for failure of RAS-targeted drugs are multifaceted, but an emerging appreciation of the complexities of RAS-mediated signal transduction has recently fed a growing consensus that a single drug that would successfully treat all RAS-mutant cancers is unlikely.\(^3-6\)

New treatment strategies have begun to challenge the perception of RAS as “undruggable.”\(^3-6\)

The discovery of inhibitors specific to KRAS mutations has generated fresh optimism about direct targeting of KRAS for a subset of patients. Meanwhile, patients with HRAS-mutant cancers could benefit from the resurrection of farnesyltransferase inhibitors (FTIs), which block the membrane association of RAS necessary for its activity.\(^3,4,6,7\)

Although FTIs were previously tested unsuccessfully in KRAS-driven tumors,\(^7,8\) the FTI tipifarnib has been given another chance by Kura Oncology.\(^9\) In a presentation at the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program, phase 2 trial results for patients with HRAS-mutant head and neck squamous cell carcinoma (HNSCC) highlighted the potential of tipifarnib.\(^10\) The FDA granted fast track designation to tipifarnib in this treatment setting,\(^11\) and numerous clinical trials for tipifarnib are ongoing in HNSCC and other malignancies.

**A MOLECULAR HUB**

RAS proteins, which exist as 4 isoforms (HRAS, NRAS, and 2 KRAS splice variants), are guanosine triphosphate (GTP)–hydrolyzing enzymes (GTPases) that cycle between a GTP-bound active form and a guanosine diphosphate (GDP)–bound inactive form, often likened to a molecular “on-off” switch. In their active form, RAS proteins serve as a molecular hub, transmitting signals from membrane-bound receptors into the cell by activating a variety of downstream pathways that regulate numerous cellular processes (FIGURE).\(^4,7,12\)

RAS activity is tightly regulated in several ways. In the absence of an extracellular signal, RAS cycles very slowly between the GDP- and GTP-bound states, but following activation of upstream growth factor receptors—EGFR being the best characterized—guanine nucleotide exchange factors (GEFs) accelerate the GDP-to-GTP exchange and activate RAS.\(^4,7,12\)

Cessation of downstream effector pathway signaling triggers the reverse reaction, which is promoted by GTPase-activating proteins that boost the intrinsic GTP-hydrolyzing activity of the RAS proteins.\(^4,7,12\)

Historically, their shared structural and mechanistic features led to the misconception that the 4 RAS proteins were functionally redundant.\(^7\) Over the decades, the different isoforms have been shown to diverge in several important ways, beginning with their regulation by...
posttranslational modifications, which control the RAS proteins’ association with cell membranes, where they can interact with downstream effectors. Although the different RAS proteins are identical in most of their amino acid sequence, they diverge most in the aptly named hypervariable region (HVR). The HVR contains a motif that is targeted for prenylation by the farnesyltransferase enzyme.\(^3\,7\,13\)

Prenylation, followed by further modification of the HVR by 2 additional enzymes, makes the carboxy-terminus hydrophobic, allowing RAS to be inserted into cellular membranes. A final modification occurs at a site in the HVR upstream of the prenylation target sequence. The type of modification, dubbed the second signal, is unique to the specific RAS isoform; for example, HRAS and NRAS undergo palmitoylation that further facilitates their membrane localization.\(^3\,7\,13\)

In another layer of regulation, RAS proteins cluster into specialized, lipid-rich domains on the plasma membrane (known as lipid rafts), which is thought to be vital to their ability to interact with specific downstream effectors. The distinct post-translational modifications that the RAS isoforms undergo cause them to associate with rafts composed of different lipids. Moreover, HRAS moves into and out of lipid rafts in a manner dependent on its activation state; GDP-bound HRAS is predominantly found in lipid rafts, whereas GTP-bound HRAS is not.\(^3\,7\,12\)

Of the downstream effectors bound by activated RAS, the most extensively studied is RAF kinase, part of the MAPK pathway; other well-known effectors include PI3K. Isoform-specific differences in RAS modification and regulation lead to activation of distinct effector pathways. For example, HRAS activates the PI3K pathway more strongly than either KRAS or NRAS. Ultimately, these signaling pathways culminate in the activation of transcription factors in the nucleus that promote gene expression to coordinate a wide variety of cellular responses, such as cell growth, survival, and proliferation. These processes, when uncontrolled, can promote oncogenesis.\(^3\,5\)

ONCOGENIC RAS

Orthologues of the RAS genes were originally identified as oncogenes that underlie the ability of certain viruses to cause cancer in rats. Seminal studies in the 1980s demonstrated that RAS genes are a vital part of the normal human genome that, when aberrantly activated, are capable of causing cancer. Since then, mutated forms of RAS proteins and members of the broader RAS superfamily have been recognized as some of the main contributors to human cancer.\(^7\,13\,14\)

One of the most common mechanisms of oncogenic RAS signaling activation is through mutations in the RAS genes themselves; however, a lack of consensus remains regarding the frequency of RAS mutations in cancer. This disparity was highlighted by a comparison of 4 major cancer mutation databases: the Catalogue of Somatic Mutations in Cancer, The Cancer Genome Atlas, Memorial Sloan Kettering’s cBioPortal for Cancer Genomics, and the International Cancer Genome Consortium. Despite considerable overlap in their data sets, these databases showed RAS mutation rates of 24.8%, 11.6%, 17.5%, and 19.3%, respectively.\(^1\)

In a recent meta-analysis, the mutation frequencies from across these data sets were used to estimate the global RAS disease burden. The authors concluded that approximately 19% of cancers harbor a RAS mutation, translating to approximately 260,000 new cases per year in the United States and 3.4 million cases globally.\(^1\)

Despite their similarities, the genes encoding the different RAS isoforms do not have equal mutation rates. Overall, KRAS mutations are the most common (found in \(\approx 75\%\) of RAS-mutant cancers), followed by NRAS (\(\approx 17\%)\); HRAS mutations, the rarest (\(\approx 7\%\)), translate into approximately 230,000 cases of HRAS-mutant cancer globally each year.\(^1\)

There is also an isoform- and cancer type-dependent distribution of RAS mutations; for example, HRAS, KRAS, and NRAS are most frequently altered in HNSCC, lung cancer, and melanoma, respectively.\(^7\,15\)

RAS mutations, which are typically missense, most often occur at several hotspots common to all 4 isoforms: the glycine residues at positions 12 (G12) and 13 (G13) and the glutamine at position 61 (Q61). Each of these mutations drives constitutive activation of the RAS protein, albeit in slightly different ways. The relative frequencies of mutations at these 3 hotspots vary by isoform; whereas 81% of KRAS mutations occur at G12 and 62% of NRAS at Q61, the different hotspots are approximately equally likely to be altered in HRAS-mutant cancers.\(^1\,4\,13\,15\)

REVIVING FTIs IN HRAS-MUTANT CANCER

Despite their importance in human cancer, oncogenic RAS mutations have long been considered undruggable. Hopes of directly targeting the proteins were abandoned early because of the lack of sites amenable to small-molecule inhibitor binding. Recently, those hopes were renewed, with

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**CLINICAL IMPLICATIONS**

**HRAS mutations**

- RAS proteins (HRAS, KRAS4A/4B, and NRAS) are central components of many cell signaling pathways.
- A recent study estimated that 19% of cancers harbor a RAS mutation, translating to approximately 3.4 million cases globally per year.
- Mutant HRAS is strongly associated with specific cancer types, including cancers of the head and neck, thyroid, bladder, and prostate.
- Farnesyltransferase inhibitors (FTIs) block membrane localization of RAS proteins, which is necessary for their activity; however, previous clinical trials in unselected patient populations proved disappointing.
- Tipifarnib, an FTI, has reemerged as a promising treatment for HRAS-mutant head and neck squamous cell carcinoma (HNSCC) with potential in other HRAS-mutant cancers.
- Eight phase 2 trials of tipifarnib in HRAS-mutant cancers are ongoing in these settings:
  - 2 basket trials (NCT04284774, NCT03155620)
  - International registration study in HNSCC (KO-TIP-007; AIM-HN/SEQ-HN; NCT03719690)
  - Relapsed/refractory (R/R) squamous non-small cell lung cancer (NCT03496766)
  - R/R urothelial carcinoma (NCT02535650)
  - R/R myelodysplastic/myeloproliferative neoplasias, including acute myeloid leukemia (NCT02807272)
  - Advanced, progressive peripheral T-cell lymphoma (NCT02464228)
  - Unresectable R/R HNSCC and squamous cell carcinoma (KO-TIP-001; NCT02383927)

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Credit: Elaine Meng/Wikimedia Commons
the development of KRAS G12C-specific inhibitors.3-7

These drugs are active only in patients with this specific mutation, but they highlight a growing consensus that the way forward for RAS targeting lies not in a single overarching strategy but in exploiting the unique nature of different types of RAS mutations, assisted by novel clinical trial designs, such as basket trials, that recruit patients with rarer mutations, such as HRAS alterations.

Over the years, a range of other strategies have been tested, including using FTIs to disrupt trafficking of RAS proteins to the membrane. Clinical trials began with tipifarnib several decades ago, but development ultimately fizzled. The failure of these early trials was largely due to resistance driven by alternative prenylation; when farnesylation was inhibited, cells used the geranylgeranyltransferase enzyme instead.4,5,8

Blocked farnesylation of HRAS cannot be rescued in this manner, which may make HRAS-mutant cancers uniquely susceptible to FTIs.7 Kura Oncology is betting on this premise; it acquired the oncology rights to tipifarnib in 2015 and is currently testing it in a range of HRAS-mutant tumors.6

The ongoing phase 2 KO-TIP-001 trial is testing tipifarnib in patients with HRAS-mutant advanced solid tumors for whom no curative therapy is available (NCT02383927). The study was originally designed to enroll patients with thyroid cancer (cohort 1) or other solid tumors (cohort 2).10

According to a presentation of preliminary results at the European Society for Molecular Oncology meeting in 2018,10 the study was amended to limit cohort 2 to patients with HNSCC and to add a third cohort of patients with other types of squamous cell carcinoma. Furthermore, only patients with a high mutant-HRAS variant allele frequency (VAF > 20%) were enrolled, and the dose was amended from 900 mg twice daily to 600 mg twice daily on a 1-week-on, 1-week-off schedule in 28-day cycles.10

At the 2020 ASCO meeting, results were presented for 21 patients with HNSCC who met the VAF criterion and had been treated to date in the KO-TIP-001 trial. Patients had received a median of 2 prior systemic regimens, including immunotherapy, chemotherapy, and/or cetuximab (Erbitux), and had experienced no response on their last therapy prior to study entry.10

Among 18 evaluable patients, the overall response rate (ORR) was 50% (95% CI, 26%-74%). Median progression-free survival (mPFS) was 5.9 months (95% CI, 3.5-19.2), and median overall survival (mOS) was 15.4 months (95% CI, 7.0-46.4).10

Results for 13 patients with recurrent/metastatic salivary gland tumors who had been treated in the original cohort 2 of this trial or an extended access program were also presented. Among 12 evaluable patients, there was 1 objective response—a partial response ongoing at 14 months—and 7 patients experienced stable disease (SD) with a median duration of 9 months, 5 of whom had greater than 10% tumor regression.10

Kura Oncology received fast track designation for tipifarnib for the treatment of HRAS-mutant HNSCC in late 2019, and an international registration study in this indication is currently recruiting patients.11 Details of the KO-TIP-007 trial (AIM-HN/SEQ-HN; NCT03719690), designed to include patients in 2 cohorts at 94 sites globally, were provided at the 2020 ASCO meeting.11

The AIM-HN cohort aims to enroll at least 59 patients with HRAS-mutant cancer, who will be treated with tipifarnib 600 mg twice daily in 28-day cycles on a 1-week-on, 1-week-off schedule. SEQ-HN is an observational cohort planning to include 225 patients with wild-type HRAS as controls, who will receive standard of care. All patients have previously received treatment, including at least 1 line of platinum-based chemotherapy for AIM-HN. A subset of patients from SEQ-HN will be matched to those treated in AIM-HN to compare the effect of HRAS mutation on responses to first-line HNSCC therapy. The company expects the trial to complete enrollment in the first quarter of 2021.11,12

Tipifarnib has also shown promise in patients with HRAS-mutant metastatic urothelial carcinoma. In a phase 2 clinical trial (NCT02535650), patients received tipifarnib 900 mg twice daily on a 1-week-on, 1-week-off schedule in 28-day cycles. Among 21 patients, 14 had an HRAS mutation (G13R, n = 7; Q61R, n = 4; G12S, n = 2; G12C, n = 1). The remaining 7 patients had wild-type HRAS but carried a polymorphism in STK11, which encodes a farnesylated tumor suppressor and was investigated as a possible target of tipifarnib.13

Patients received a median of 2 prior lines of chemotherapy, and 2 patients had received prior immunotherapy. Investigators observed 5 clinical responses among 16 evaluable patients, for an ORR of 24%; the median duration of response was 8.8 months (95% CI, 3.8-13.8). In addition, 4 patients achieved SD, mPFS and mOS were 4.7 months (95% CI, 2.5-5.6) and 6.1 months (95% CI, 5.0-7.2), respectively.13

Only 1 responder had an STK11 polymorphism, and this patient was later found to have a nonsense mutation in HRAS; thus, there were no responses in patients with wild-type HRAS. The investigators concluded that tipifarnib is not effective in patients with the STK11 polymorphism and/or wild-type HRAS.14

Jane de Lartigue, PhD, is a freelance medical writer and editor based in Gainesville, Florida.

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

Saba Analyzes Potential for Tipifarnib in HNSCC

Nabil F. Saba, MD, discusses the clinical implications of targeting HRAS-mutant head and neck squamous cell carcinoma (HNSCC) with tipifarnib, a small molecule inhibitor of farnesyltransferase, a critical enzyme needed for HRAS activation.

Saba is director of the Head and Neck Medical Oncology Program at Winship Cancer Institute of Emory University, and professor in the Department of Hematology and Medical Oncology and Department of Otolaryngology at Emory University School of Medicine, both in Atlanta, Georgia.

View Video: https://bit.ly/36sWCqP
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 status.

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 patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 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. 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.

Please see additional Important Safety Information on the adjacent page.
T O CHEMOTHERAPY
IF SHE RESPONDS
on baseline weight or platelet count, Grade ≥3
administered a starting dose of ZEJULA based
2%, and 2% of patients. In patients who were
and neutropenia occurred, respectively, in 4%,
39%, 31%, and 21% of patients receiving ZEJULA.
incidence of Grade ≥3 thrombocytopenia, anemia,
patients receiving ZEJULA. In PRIMA, the overall
anemia and neutropenia) have been reported in
thrombocytopenia, Hypertension and hypertensive crisis
have been
hematologist for further investigations.
and periodically thereafter. If hematological toxicities
receiving ZEJULA vs 1% of patients receiving placebo,
Grade 3-4 hypertension occurred in 6% of patients
reported in patients receiving ZEJULA. In PRIMA,
PRIMA were thrombocytopenia (66%), anemia,
neutrophils (66%), decreased lymphocytes (51%),
increased alkaline phosphatase (46%), increased
creatinine (40%), decreased magnesium (56%),
increased AST (35%) and increased ALT (29%).
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 (56%),
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/HCP to explore the PRIMA data
Trademarks are property of their respective owners.
©2020 GSK or licensor.
NRP-JRMA2000007 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 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, 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, 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 1-4 hypertension occurred in 6% of ZEJULA-treated patients, compared to 2% 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 weeks (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 1-4 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 QUADRA, Grade 1-4 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, then 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].

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) of full prescribing information]. ZEJULA has the potential to cause teratogenicity and/or embryofetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) 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 8 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 labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia [see Warnings and Precautions (5.1)]
- 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 1814 patients who received ZEJULA in the pooled PRIMA, NOVA and QUADRA trials were nausea (65%), thrombocytopenia (65%), anemia (56%), fatigue (55%), constipation (55%), mucositis (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspepsia (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dyspnea (14%), acute kidney injury (13%), urinary tract infection (12%), and hyponatremia (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: 0.39 to 29 months).

Serious adverse reactions occurred in 12% of patients receiving ZEJULA. Serious adverse reactions in ≥2% of patients were thrombocytopenia (16%), anemia (16%), and small intestinal obstruction (2.6%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (see patient each).

Permanental discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in ≥1% of patients who received ZEJULA included thrombocytopenia (5.2%), anemia (5.2%), nausea and neutropenia (4.1% each). Adverse reactions led to dose reduction or interruption in 40% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

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

<table>
<thead>
<tr>
<th>Table 1. Adverse Drug Reactions Reported in ≥1% of All Patients Receiving ZEJULA in PRIMA*</th>
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<th>Grades 3-4*</th>
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<td>Placebo Nuqo44 %</td>
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</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>13</td>
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<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>13</td>
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<tr>
<td>Cough</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>7</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.

**CICAE Common Terminology Criteria for Adverse Events version 4.02 includes neutropenia, neutropenic infection, neutropenia sepsis, febrile neutropenia.

**Includes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

**Includes blood creatine increased, blood bilirubin increased, acute kidney injury, renal failure, blood creatinine increased.
### Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEULA in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grades 3-4</th>
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<tbody>
<tr>
<td>ZEULA</td>
<td>Placebo</td>
</tr>
<tr>
<td>ZEULA N=848</td>
<td>Placebo N=524</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
</tr>
<tr>
<td>Increased neutrophils</td>
<td>66</td>
</tr>
<tr>
<td>Increased lymphocytes</td>
<td>51</td>
</tr>
<tr>
<td>Increased erythrocytes</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>36</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 3: Adverse Reactions Reported in ≥15% of Patients Receiving ZEULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA</td>
<td>Placebo</td>
</tr>
<tr>
<td>ZEBULA N=169</td>
<td>Placebo N=86</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>70</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>63</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63</td>
</tr>
<tr>
<td>Increased neutrophils</td>
<td>60</td>
</tr>
<tr>
<td>Increased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>43</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>41</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>31</td>
</tr>
</tbody>
</table>

### 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>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA</td>
<td>Placebo</td>
</tr>
<tr>
<td>ZEULA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>59</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>26</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEULA</td>
<td>Placebo</td>
</tr>
<tr>
<td>ZEULA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>Blood and Lymphoid System Disorders</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>50</td>
</tr>
</tbody>
</table>
Treatments of Advanced Ovarian Cancer After Three or More Chemotherapies

The safety of ZELVA, monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 465 patients with recurrent high-grade serous epithelial 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: 0.01 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

Fetal adverse reactions occurred in 7% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZELVA, Serious adverse reactions in >1% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 4) occurred in 21% of patients who received ZELVA.

Adverse reactions led to dose reduction or interruption in 33% of patients receiving ZELVA. The most common adverse reactions occurring in ≥5% and leading to dose reduction or interruption were neutropenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (5%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZELVA in QUADRA.

### Table 7: Adverse Reactions Reported in ≥10% of Patients Receiving ZELVA in QUADRA

<table>
<thead>
<tr>
<th>Category</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Percent</td>
<td>Percent</td>
</tr>
<tr>
<td>Anemia</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>0.2</td>
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<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>56</td>
<td>7</td>
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<tr>
<td>Infections and Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>2</td>
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<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
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<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
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<td></td>
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<tr>
<td>Musclekeletal pain</td>
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<td>3</td>
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<tr>
<td>Nervous System Disorders</td>
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<tr>
<td>Headache</td>
<td>19</td>
<td>0.4</td>
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<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
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<tr>
<td>Psychiatric Disorders</td>
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<tr>
<td>Insomnia</td>
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<td>1</td>
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<tr>
<td>Renal and Urinary Disorders</td>
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<tr>
<td>Acute kidney injury</td>
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<td>1</td>
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<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
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<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

*CIDAE=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, ZELVA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (13.1) of full prescribing information).

### 8.5 Geriatric Use

In PREMA, 39% 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 ZELVA 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 ZELVA 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 (NCI-ODWG) criteria. The safety of ZELVA in patients with moderate to severe hepatic impairment is unknown.

### 10 OVERDOSE

There is no specific treatment in the event of ZELVA 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).

**MEGUM**

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 ZELVA (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 ZELVA (see Dose and Administration (2.2) of full prescribing information). ZELVA should be taken once daily. Instruct patients that if they miss a dose of ZELVA, not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZELVA 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 (5.1)).

**Contraception**

Advise females of reproductive potential to use effective contraception during treatment with ZELVA 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 ZELVA and for 1 month after the last dose (see Use in Specific Populations (8.3)).

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NPR/IN2320007 August 2020

Produced in USA.
Frontline Treatment Arsenal Expands in Advanced HCC

by CHRISTINA T. LOGUIDICE

HEPATOCELLULAR CARCINOMA (HCC) is the fourth most-common cause of cancer-related death worldwide. Although rates of HCC incidence started to plateau in 2013, many cases continue to be diagnosed at more advanced stages, especially in patients without liver disease. Despite the number of HCC cases, treatment options for patients with advanced disease remain sparse. However, several new drug approvals in the frontline setting and the initiation of numerous trials exploring novel strategies are seeking to change the tides for aggressive cancer. During an OncLive Peer Exchange®, a panel of liver cancer experts reviewed the available systemic treatments and how they choose between them. They also shared their thoughts on some of the ongoing clinical trials that have the potential to reshape the treatment landscape in the coming years.

FDA-APPROVED FRONTLINE TREATMENTS

There are 3 FDA-approved frontline treatment options for patients with unresectable HCC and Child-Pugh class A liver function: tyrosine kinase inhibitor (TKI) sorafenib (Nexavar), approved in 2008; TKI lenvatinib (Lenvima), approved in 2018; and immunotherapy with atezolizumab (Tecentriq) and bevacizumab (Avastin), approved in 2020.

“Most of us will remember the days before sorafenib, where Megace [megestrol acetate], tamoxifen, or another unproven agent would be used because we were so desperate for systemic agents in this disease,” Tanios S. Bekaii-Saab, MD, said. He noted that sorafenib was approved based on data from the SHARP trial (NCT00105443), which showed an approximate 3-month benefit with sorafenib versus placebo in median overall survival (OS; 10.7 vs 7.9 months) and median time to radiologic progression (5.5 vs 2.8 months). Although sorafenib was the first drug to show a survival benefit in patients with advanced HCC, “the dose was challenging, and everyone came up with their own dosing schedule and regimen to reduce the risk of toxicities,” Bekaii-Saab said, adding that there were many attempts to find better-tolerated and more-efficacious agents, but little progress was made until 10 years later when lenvatinib was approved based on data from the REFLECT trial (NCT01761266).

Investigators of REFLECT, a phase 3, international, multicenter, open-label noninferiority study randomized 954 patients with previously untreated metastatic or unresectable HCC to lenvatinib (n = 478) or sorafenib (n = 476). The median OS was 13.6 months with lenvatinib compared with 12.3 months with sorafenib (HR, 0.92; 95% CI, 0.79-1.06). In addition to its noninferior survival, lenvatinib demonstrated an improved median progression-free survival (PFS; 7.3 vs 3.6 months; HR, 0.64; 95% CI, 0.55-0.75). Based on these data and its tolerable safety profile, lenvatinib was the favored regimen until the approval of the atezolizumab/bevacizumab combination, Bekaii-Saab noted. The approval was based on data from IMbrave150 (NCT03434379), a global, phase 3 trial that randomly assigned 501 treatment-naïve patients with unresectable HCC to receive atezolizumab/bevacizumab (n = 336) or sorafenib (n = 165). The primary
end points included OS and PFS in the intention-to-treat population, as assessed by independent review. “This study came and hit every single one of the end points, and resulted in very impressive hazard ratios,” Bekaii-Saab said. At the time of the primary analysis in August 2019, the HR for death with the immunotherapy combination versus sorafenib was 0.58 (95% CI, 0.42-0.79; \( P < .001 \)). Although the OS has yet to be reported, the 12-month OS rate was 67.2% (95% CI, 61.3%-73.1%) in the atezolizumab/bevacizumab arm versus 54.6% (95% CI, 45.2%-64.0%) in the sorafenib arm. The median PFS was 6.8 months (95% CI, 5.7-8.3) and 4.3 months (95% CI, 4.0-5.6) in the respective groups (HR, 0.59; 95% CI, 0.47-0.76; \( P < .001 \)).

“Most importantly, [atezolizumab/bevacizumab] preserves and improves the quality of life (QOL) of the patients,” Bekaii-Saab said, noting that the study also looked at various patient-reported outcomes as secondary end points. Patients completed the European Organisation for Research and Treatment of Cancer (EORTC) QLO-C30 and the EORTC QLO-HCC18 questionnaires before treatment, every 3 weeks during treatment, and every 3 months after treatment discontinuation or disease progression. More than 90% of patients completed the questionnaires. Compared with sorafenib, the immunotherapy combination delayed time to deterioration (TTD) of patient reported QOL, physical functioning, and role functioning (TABLE 10). Atezolizumab/bevacizumab also delayed TTD in patient-reported appetite loss, fatigue, pain, and diarrhea, with fewer patients in the immunotherapy arm versus the sorafenib arm experiencing clinically meaningful deterioration in any of these symptoms.

“They have a much better quality of life, and they can maintain their work and activity. In a situation where we are talking about palliation, although their life span is still limited, it makes quite a difference whether their quality of life is good or impaired, and this is very in favor of this combination in terms of improvement of quality of life and other aspects,” Peter R. Galle, MD, PhD, said.

### TABLE. Patient-Reported Outcomes From the IMbrave150 Trial 10

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atezolizumab/bevacizumab</th>
<th>Sorafenib</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTD of patient-reported QOL, months</td>
<td>11.2</td>
<td>3.6</td>
<td>0.63 (0.44-0.85)</td>
</tr>
<tr>
<td>TTD of physical functioning, months</td>
<td>13.1</td>
<td>4.9</td>
<td>0.53 (0.39-0.73)</td>
</tr>
<tr>
<td>TTD of role functioning, months</td>
<td>9.1</td>
<td>3.6</td>
<td>0.62 (0.46-0.84)</td>
</tr>
</tbody>
</table>

QOL, quality of life; TTD, time to deterioration.

### SELECTING BETWEEN FRONTLINE TREATMENTS

The panelists agreed that the standard of care for fit patients with Child-Pugh A liver function and advanced HCC is now atezolizumab/bevacizumab; however, Pierre Gholam, MD, noted that bleeding is an issue with certain patients. “[Risk of bleeding] would probably be one of the top 2 or 3 most-asked questions when it comes to atezolizumab/bevacizumab therapy,” Gholam said. “How might one manage or mitigate the risk of bleeding in the setting of cirrhosis? An important thing to remember and consider is that the risk of having varices or, perhaps more importantly, large varices, increases as the Child-Pugh score increases. Someone with Child-Pugh score C is much more likely to have large varices than patients with Child-Pugh B, and they are much more likely to have varices than patients with Child-Pugh A.” But Gholam said the risk of progression for varices is approximately 7% to 10% and that they are compounded by other factors such as uncontrolled alcohol use. Addressing these variances without delaying treatment to mitigate the risk of bleeding would include screening for the presence of large varices rapidly.

Treatment decisions are much more challenging in patients who are not candidates for this regimen. “If I were asked to summarize the patients for whom we wouldn’t use atezolizumab plus bevacizumab, I would generally categorize them into 3 or 4 different types,” R. Katie Kelley, MD, said. These patients would include those who were excluded from the IMbrave150 trial, such as those with active varices or who are at higher risk for bleeding varices or other types of bleeding based on their screening, endoscopy, or other clinical factors; patients with Child-Pugh B liver function; and patients with autoimmune disease or history of transplantation, she said. “When making [treatment decisions] for these groups of patients who aren’t good candidates for atezolizumab plus bevacizumab, we can look to lenvatinib and sorafenib.”

When deciding between sorafenib and lenvatinib for these patients, Kelley said she considers the collective clinical trial data, including subgroup analyses. “If it’s a patient with Child-Pugh B liver function, then it’s important to note that we don’t have prospective data for lenvatinib. . . . so I’m more likely to choose sorafenib with an empiric starting dose reduction based on some of the VA [US Department of Veterans Affairs] data that have been published,” she said.

Although Kelley said it may be reasonable to try a checkpoint inhibitor-based regimen in some patients with autoimmune deficiencies, if there is close monitoring, this does not apply to patients with active disease requiring immunosuppression or those who received a liver transplant. She noted that the risk of graft loss is too high in the latter group, with studies reporting a risk of rejection greater than 30%. In such patients, she said sorafenib and lenvatinib are both reasonable choices and that the adverse effects profiles of these agents should be considered and weighed against the patient’s comorbidities and medications. “Lenvatinib does have more QTc [corrected QT interval] prolongation risk than sorafenib,” Kelley said. Subsequently, if a patient is on a medication that may interact with lenvatinib to cause this complication, she said she would select sorafenib.
Another common question, Kelley said, is whether treatment decisions may hinge on patients’ viral status, notably whether they are infected with hepatitis B versus hepatitis C. “[If you] look at the REFLECT trial of sorafenib versus lenvatinib and the forest plots, the survival is similar, and there was no significant difference in the subset analyses for hepatitis B versus hepatitis C. There was a trend toward benefit for lenvatinib for time to progression and PFS for both viral subgroups; perhaps it was more pronounced for those with hepatitis B,” she said. Kelley cautioned that subgroup analyses are not adequately powered to provide definitive answers, but they do provide some insights. “Overall, I would say that we don’t have enough data to make a strong decision based on viral status. Perhaps lenvatinib should be favored in patients with hepatitis B, but we can’t choose the drug based on hepatitis C status 1 way or the other. It should be based more on comorbidities than viral status,” she said.

A ROLE FOR NIVOLUMAB?

Nivolumab (Opdivo) is approved as a single agent or in combination with ipilimumab (Yervyoy) for patients with advanced HCC who have previously been treated with sorafenib. Although not approved in the frontline setting, the National Comprehensive Cancer Network (NCCN) hepatocellular carcinoma guidelines note that it can be a useful first-line systemic therapy in certain circumstances, notably for patients ineligible for TKIs or other antiangiogenic agents.

Kelley explained that there are patients who might otherwise not have a good treatment option. “I’ve had a few patients who have nonhealing wound complications after surgery, for example. I have also had patients who have a significant thrombotic predisposition or have had clots that are intractable on antiangiogenic therapy. There are some patients for whom we can’t use antiangiogenic therapies, and there are also some patients with poor-risk Child-Pugh B for whom we may not feel comfortable using some of our other agents,” she said.

Second, she explained that nivolumab does not have the same risk of antiangiogenic toxicity or comorbidity as the TKIs or bevacizumab and that there are some prospective data for patients with Child-Pugh B status that are reassuring. “The NCCN guideline inclusion reflects the fact that there are safety data for nivolumab in these contexts and that, whereas the CheckMate 459 [NCT02576509] frontline trial of sorafenib vs nivolumab did not meet its end points and was a negative study, we also know that there was a trend toward benefit, with the caution of interpreting trends such as that. But we have the second-line data from CheckMate 040 [NCT01658878] that led to an FDA approval in the second-line setting,” she said. Ultimately, the panelists agreed that lenvatinib or sorafenib are preferable for patients who are candidates for these agents, but that nivolumab is a reasonable choice for patients who have no other category 1 options available, as may be the case for a patient with an open chest wall wound from a poor surgical outcome.

PROMISING FUTURE DIRECTIONS

“There is a lot of exciting stuff coming down the pike,” moderator Richard S. Finn, MD, said, noting that the frontline treatment landscape for HCC is poised to continue rapidly evolving after a decade of stagnation. One exciting approach being explored is combining a TKI with a checkpoint inhibitor.

This combination is being assessed in 2 phase 3 trials: LEAP-002 (NCT03713593) and COSMIC-312 (NCT03755791), the latter of which is still recruiting patients.

LEAP-002 is comparing lenvatinib and pembrolizumab (Keytruda) with lenvatinib monotherapy. Data are not yet available, but the combination showed promise in other clinical trials, with Finn noting response rates of approximately 36% in the frontline treatment of patients with Child-Pugh A. He also noted that thus far the safety data for the combination look consistent with single-agent lenvatinib or single-agent pembrolizumab.

The COSMIC-312 trial is comparing the safety and efficacy of first-line cabozantinib (Cabometyx) plus atezolizumab with sorafenib in patients with advanced HCC and will include a single-agent cabozantinib arm for comparison with single-agent sorafenib. Cabozantinib is already approved as a monotherapy in patients previously treated with sorafenib. COSMIC-312 is randomly assigning approximately 740 eligible patients 2:1:1 to receive the combination (approximately 370 patients) or 1 of the single agents (estimated 185 patients in each arm). “[The hypothesis is] based on the rationale that cabozantinib has some interesting tyrosine kinase inhibition that may be immunomodulatory in a different way,” Kelley said. An article Kelley coauthored in Future Medicine notes that cabozantinib targets multiple receptor kinases involved in angiogenesis, tumor growth, and metastasis, including VEGF, MET, and the TAM family of receptor kinases (TYRO3, AXL, MER). Kelley said that the cabozantinib/atezolizumab combination recently showed promising results in renal cell carcinoma, with an objective response rate of nearly 50%.

“The premise that not only is there a potential for additive benefit or synergy when you combine antiangiogenic therapy with immunotherapy, but these TKI therapies can also be immunomodulatory in the microenvironment and promote an immune response in other ways, such as by inhibiting other kinase pathway signaling and conferring potential for additive effect, being active drugs in their own right,” Kelley said.

Two phase 3 trials also are exploring another immunotherapy approach that combines CTLA-4 inhibition with a checkpoint inhibitor. Kelley noted that the rationale for this combination stems from promising results in other solid tumors, including lung cancer and melanoma, which showed synergy in the immune response. The trials examining this combination in patients with advanced HCC include HIMALAYA (NCT03298431) and CheckMate 9DW (NCT04039607), the latter of which is still recruiting patients.

“There are now 4 ongoing phase 3 studies in the frontline setting, after the approval for atezolizumab/bevacizumab, which speaks to the fact that there’s been incredible interest and excitement in liver cancer,” Finn said. “Having been in the space for some time, it’s exciting to be able to sit down with a patient and tell them all the great options we have that are improving survival and that we can expect responses to their tumor,” he said.
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