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

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BLMJRNA200002 August 2020
Produced in USA.

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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 ophtalmic 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 (14) of full Prescribing Information].

This indication may be contingent upon verification and description of clinical benefit [see Clinical Studies (14) of full Prescribing Information]. Continued approval for [see Clinical Studies (14) of full Prescribing Information].

This indication is approved under accelerated approval based on response rate [see Clinical Studies (14) of full Prescribing Information].

This indication is approved under accelerated approval based on response rate [see Clinical Studies (14) of full Prescribing Information].

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><strong>Grade 1</strong> Corneal examination finding(s): Moderate superficial keratopathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.</td>
</tr>
<tr>
<td>Change in BCVA: Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200</td>
<td>Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia [see Warnings and Precautions (5.5)]</td>
<td>Platelet count less than 25,000/mL</td>
<td>Consider withholding BLENREP and/or reducing the dose of BLENREP.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reactions [see Warnings and Precautions (5.4)]</td>
<td>Grade 2 (moderate) or Grade 3 (severe)</td>
<td>Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 4 (life-threatening)</td>
<td>Permanently discontinue BLENREP and provide emergency care.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 3</td>
<td>Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 4</td>
<td>Consider permanent discontinuation of BLENREP if continuing treatment, withhold BLENREP until improvement to Grade 1 or better and resume at reduced dose.</td>
</tr>
</tbody>
</table>

2.4 Preparation and Administration

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

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

**Reconstitution**

- Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (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 vial(s).
• If the diluted infusion solution is not used immediately, store refrigerated at
36°F to 46°F (2°C to 8°C) 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 (68°F to 77°F [20°C to 25°C]) 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 polyethersulfone (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 infective keratitis) have been reported. Most keratopathy events developed within
the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients
with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1
or lower after median follow-up of 6.2 months. Of the 61% who had ongoing
keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the
follow-up ended due to death, study withdrawal, or lost to follow up. For patients in
whom events resolved, the median time to resolution was 2 months (range: 11 days
to 83 months).

Visual Acuity Changes
A clinically significant decrease in visual acuity of worse than 20/40 in the better-
seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the
better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than
20/40, 89% resolved and the median time to resolution was 22 days (range: 7
to 42 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 ophthalmologic 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.

5.2 BLENREP REMS
BLENREP is available only through a restricted program under a REMS called
the BLENREP REMS because of the risks of ocular toxicity [see Warnings and
Precautions (5.1)].
Notable requirements of the BLENREP REMS include the following:
• Prescribers must be certified with the program by enrolling and completing
training in the BLENREP REMS.
• Prescribers must counsel patients receiving BLENREP about the risk of ocular
toxicity and the need for ophthalmic examinations prior to each dose.
• Patients must be enrolled in the BLENREP REMS and comply with monitoring.
• Healthcare facilities must be certified with the program and verify that patients
are authorized to receive BLENREP.
• Wholesalers and distributors must only distribute BLENREP to certified healthcare
facilities.
Further information is available, at www.BLENREPREMS.com and
1-855-209-9188.

5.3 Thrombocytopenia
Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population,
including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse
Reactions (6.1)]. The median time to onset of the first thrombocytopenic event
was 28.5 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 predmedication
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 dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the
recommended dose) administered intravenously once every 3 weeks in 218 patients
in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved
dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were
exposed for 6 months or longer.

(continued on next page)
Relapsed or Refractory Multiple Myeloma

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

Serious adverse reactions occurred in 40% of patients who received BLENREP.

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

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

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

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

The most common adverse reactions (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received BLENREP. 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-glutamyl transferase increased.

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

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

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.

(continued from previous page)
• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
• Advise patients to administer preservative-free lubricant eye drops as needed to relieve dryness.

• Advise patients that ocular toxicity may occur during treatment with BLENREP. Patients should be monitored for keratopathy.

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

17 PATIENT COUNSELING INFORMATION

15 REFERENCES

[see Clinical Pharmacology (12.3) of full Prescribing Information]

moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years or older.

 males. The effects were not reversible in male rats, but were reversible in female rats.

Advise women of reproductive potential to use effective contraception after the last dose of BLENREP.

8.3 Females and Males of Reproductive Potential

8.2 Lactation

BLENREP is available only through a restricted program called BLENREP REMS.

8.1 Pregnancy

[see Warnings and Precautions (5.1)]

BLENREP is an injected cancer drug that is used to treat some types of cancer.

The recommended dose is 10 mg/kg given intravenously over 1 hour as an initial dose, followed by weekly doses of 10 mg/kg over 24 hours.

Thrombocytopenia

• Patients must comply with ongoing monitoring for eye exams and vision.

[see Warnings and Precautions (5.2)]

• Patients must comply with ongoing monitoring for eye exams and vision.

[see Warnings and Precautions (5.1)]

BLENREP may adversely affect their vision.

[see Warnings and Precautions (5.1)]

• Patients must comply with ongoing monitoring for eye exams and vision.

[see Warnings and Precautions (5.1)]

8.6 Renal Impairment

Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether the effectiveness differs compared with that of younger patients.

[see Clinical Pharmacology (12.3) of full Prescribing Information]

Males:

Because of the potential for genotoxicity, advise males with female partners to keep their female partners pregnant during treatment with BLENREP.

[see Warnings and Precautions (5.1)]

Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

[see Nonclinical Toxicology (13.1) of full Prescribing Information].

Fertility

• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

[see Nonclinical Toxicology (13.1) of full Prescribing Information].

Males:

Because of the potential for genotoxicity, advise males with female partners to keep their female partners pregnant during treatment with BLENREP.

[see Warnings and Precautions (5.1)]

Advise women of reproductive potential to use effective contraception after the last dose of BLENREP.

[see Warnings and Precautions (5.1)]

8.3 Females and Males of Reproductive Potential

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[see Warnings and Precautions (5.1)]

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[see Warnings and Precautions (5.1)]

Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

[see Nonclinical Toxicology (13.1) of full Prescribing Information].

Fertility

• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

[see Nonclinical Toxicology (13.1) of full Prescribing Information].

Males:

Because of the potential for genotoxicity, advise males with female partners to keep their female partners pregnant during treatment with BLENREP.

[see Warnings and Precautions (5.1)]

Advise women of reproductive potential to use effective contraception after the last dose of BLENREP.

[see Warnings and Precautions (5.1)]

8.3 Females and Males of Reproductive Potential

8.2 Lactation

BLENREP is available only through a restricted program called BLENREP REMS.
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 61.
Immunotherapy: Expert Puts Fresh Focus on AEs

by LARRY HANOVER

Mario Szolov, MD, whose research has helped define the field of immune checkpoint therapy, discusses the importance of appropriately addressing adverse effects (AEs) in patients who receive these agents. The upcoming 5th Annual International Congress on Immunotherapies in Cancer® will focus on practical questions that arise in the administration of these agents.
ICI Era Requires a Road Map

THERE WAS MUCH REJOICING in March 2011 when the FDA approved ipilimumab (Yervoy) for patients with unresectable or metastatic melanoma. The decision launched the immune checkpoint inhibitor (ICI) era and helped validate the concept that immunotherapeutic strategies could be used against cancer.

Few could have predicted, however, the way in which ICIs would make inroads into the treatment paradigms for so many malignancies. As we near the 10th anniversary of the ipilimumab decision, ICIs that target the PD-1/PD-L1 pathway are approved in various clinical settings for 18 tumor types plus 2 biomarker-driven indications across solid tumors. Additionally, ipilimumab, a CTLA-4 inhibitor, is approved in 6 tumor types.

That’s an impressive track record by any yardstick. However, as Mario Sznol, MD, notes in the cover story in this issue of OncologyLive®, translating these therapies into clinical practice has proved challenging. Sznol, of course, knows more than almost anyone about ICI therapies. The current president of the Society for Immunotherapy of Cancer (SITC), Sznol has been a key investigator into anti–PD-1/PD-L1 antibodies and ipilimumab, both in early and later phases, and still spends half his time seeing patients in clinic.

It is noteworthy, therefore, that the 5th Annual International Congress on Immunotherapies in Cancer®, a live virtual meeting that Sznol is cochairing along with Naiyer A. Rizvi, MD, on December 12, will focus on practical applications of administering ICIs and adoptive T-cell therapies. Integrating these agents into treatment landscapes requires many adjustments. Although it is well established that immunotherapies have toxicity profiles that are different from those of traditional chemotherapies, the spectrum of immune-related adverse events is complex and nuanced.

SITC and the American Society of Clinical Oncology have developed detailed guidelines for tackling these toxicities. The immunotherapy conference, hosted by Physicians’ Education Resource®, LLC (PER®), offers an opportunity to engage with the experts who helped define the field. For further information, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
OncLive® is proud to present

The 2020 Giants of Cancer Care® Honorees

A Selection Committee of more than 120 eminent oncologists have chosen honorees from several tumor types and specialty categories who have achieved landmark successes within the global field of oncology, improved cancer care, and established the building blocks for future advances.

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Université Libre de Bruxelles/Jules Bordet Institute

**CANCER DIAGNOSTICS**
Laura J. van’t Veer, PhD
University of California San Francisco
Helen Diller Family Comprehensive Cancer Center

**COMMUNITY OUTREACH/CANCER POLICY**
Clifford A. Hudis, MD
American Society of Clinical Oncology

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University of California San Francisco
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**GASTROINTESTINAL CANCER**
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University of California San Francisco
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**LUNG CANCER**
Tony S.K. Mok, MD
The Chinese University of Hong Kong

**LYMPHOMA**
George P. Canellos, MD
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**MELANOMA & OTHER SKIN CANCERS**
Keith T. Flaherty, MD
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**MYELOMA**
Sagar Lonial, MD
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**PREVENTION/GENETICS**
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The University of Texas MD Anderson Cancer Center

Register today to honor these individuals for their remarkable achievements in oncology research and clinical practice.

Register now at giantsofcancercare.com/rsvp.
**From the Editor**

**Complex Clinical Trial Issues Require an Ethical Balancing Act**

*by MAURIE MARKMAN, MD*

These are complex times for the clinical research community. The fundamental objectivity of major scientifically oriented public health agencies has been called into question, while the issue of what constitutes sufficient evidence for a therapeutic strategy to be considered “standard” is also being challenged.¹

These dilemmas highlight a related question faced by oncologists who participate in clinical trials and, most importantly, who are required to explain to patients why participation in a given cancer study may be important for them to consider.

The current discussion highlighted in news reports regarding the validity of retrospective or prospective observational studies versus therapy specifically determined through the process of randomization is at the core of the debate regarding the clinical utility of convalescent plasma in the management of coronavirus disease 2019.²

In fact, the argument is similar to a discussion that may occur commonly in the practice of an oncologist who elects to participate in clinical trial research. Although the decision to become research subjects in investigative efforts is—and must always be—made by the individual patient with cancer themselves, when physicians consider asking patients whether they might be interested in participating in a therapeutic study, these professionals are surely also asking themselves whether a trial would be in the patient’s best interest.

It is here where we directly confront the complex but critically relevant issue of equipoise. As magnificently articulated in the landmark essay by Samuel and Deborah Hellman in the *New England Journal of Medicine* almost 30 years ago, the fundamental roles of the (a) physician and (b) the physician–clinical scientist differ—at times substantially: “The physician, by entering into a relationship with an individual patient, assumes certain obligations, including the commitment always to act in the patient’s best interests .... The clinical scientist is concerned with answering questions—i.e., determining the validity of formally constructed hypotheses. Such scientific information, it is presumed, will benefit humanity in general.”

The clinician’s dilemma occurs in the potential conflict between these 2 most often complementary but, unfortunately, surely not identical goals. The authors wrote: “The ethical obligation created by the covenant between doctor and patient requires the doctor to see the interests of the individual patient as primary and compelling. In essence, the doctor-patient relationship requires doctors to see their patients as bearers of rights who cannot be merely used for the greater good of humanity.”²

If we accept the primacy of this clearly articulated role of an oncologist, under what circumstances would it be ethically acceptable for that clinician to permit a patient with cancer to be randomized to one therapeutic approach versus another?

It is here that the concept of equipoise comes into play. As noted by the Hellmans, if participation by a specific patient in a given randomized clinical trial is to be considered an acceptable therapeutic option, it is essential that “the physician believes that the severity and likelihood of harm and good are evenly balanced.”² Conversely, when considering possible alternative strategies and potentially available novel approaches in disease management “if, however, he or she believes that the new treatment may be either more or less successful or more or less toxic, the use of randomization is not consistent with fidelity to the patient.”²

Clearly these are very strong statements, but assuming we accept the basic foundational argument differentiating the role of the physician from that of the clinical-scientist, obvious questions follow. For example, would it be ethical for an oncologist to enter a patient into a randomized
From the Editor

clinical trial if one of the arms of the study included a standard-of-care antineoplastic drug delivered at what is known to be a potentially excessive toxic dose/schedule, such that the clinician would not administer this specific regimen to patients who were not participants in this randomized study?

In fact, this was precisely the situation in the oncology regulatory clinical trials arena for a number of years when single-agent pegylated liposomal doxorubicin was delivered at a dose of 50 mg/m² (once every 4 weeks) as a control arm in a number of ovarian cancer studies in platinum-resistant disease when it was well recognized that this dose level was rarely—if ever—administered in noninvestigative clinical practice. Considering the issue of equipoise, the question is whether a physician who was also serving as a clinical investigator on such a study was truly acting in their patients’ best interests if they suggested or encouraged patients to become research subjects in these studies.

Fortunately, the highly disturbing ethical concerns associated with these historical ovarian cancer studies are most uncommon today in the realm of oncology clinical trials. However, clinical cancer investigators are frequently called on to consider recommending possible entry of patients into an investigative effort and they must weigh whether participation is truly the optimal therapeutic option for an individual patient at a specific point in their cancer journey.

Further, oncologists must seek to navigate carefully the ongoing intense debate within the cancer community regarding the required level of evidence to permit novel alternative strategies to become an acceptable standard of care. For example, how does an individual oncologist view the clinically impressive results of a nonrandomized experience from a major academic center published in a high-impact medical journal in evaluating the issue of equipoise?

Additionally, many situations exist in which promising anticancer agents may be available only through participation in FDA-sanctioned randomized trials, where in the opinion of the patient’s oncologist the decision to deliver the superior therapeutic strategy may have to be left to the luck of the draw.

Despite these complexities, or perhaps because of them, clinicians should carefully consider the issue of equipoise, as viewed by individual oncologists based on their clinical knowledge and experience as well as their intimate understanding of the patient’s medical history and personal goals, when any individual is to be offered participation in an investigative effort.

The fact that a study is open at the oncologist’s institution and a patient meets eligibility criteria should only be the starting point in thoughtful consideration and subsequent discussion of the appropriateness of this possible therapeutic option.

REFERENCES

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\(^1\text{-}^3\)

**Indication**

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

**Important Safety Information**

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

**Hematologic adverse reactions** (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 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,
PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS \(^1\)\(^4\)

**OVERALL POPULATION**

38% REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH

**HRD POPULATION**

57% REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH

**Important Safety Information (continued)**

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

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

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

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


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

Visit ZEJULA.COM/HCP to explore the PRIMA data

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Produced in USA.

Please see Brief Summary on the following pages.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

ZEJULA (niraparib) capsules, for oral use

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

1. INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

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

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

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

1.3 Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

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

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZEJULA monotherapy in clinical trials. In 1975 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

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

5.2 Bone Marrow Suppression

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

In PRIMA, the overall incidence of Grade 3 or Grade 4 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 35%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade 3 or Grade 4 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. In NOVA, Grade 3 or Grade 4 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 29% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients. In QUADRIVA, Grade 3 or Grade 4 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 1% of patients.

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 QUADRIVA trials were nausea (65%), thrombocytopenia (65%), anemia (56%), fatigue (55%), constipation (19%), musculoskeletal pain (18%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

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

Table 1. Adverse Drug Reactions Reported in ≥5% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEJULA</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N/A %</td>
<td>N/A %</td>
</tr>
<tr>
<td></td>
<td>N/A %</td>
<td>N/A %</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>Investigations</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle and joint pain</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>13</td>
</tr>
<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 Uremic 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>
</tr>
<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.

*CTCAE: Common Toxicity 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 area increased, acute kidney injury, renal failure, blood creatine increased.
Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELENA IN PRIMA

<table>
<thead>
<tr>
<th></th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELENA N=169</td>
<td>Placebo N=244</td>
<td>ZELENA N=169</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>77%</td>
<td>37%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71%</td>
<td>36%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>25%</td>
<td>63%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51%</td>
<td>29%</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>46%</td>
<td>21%</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>40%</td>
<td>23%</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>25%</td>
<td>46%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35%</td>
<td>17%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Patients Receiving ZELENA with Dose Based on Baseline Weight or Platelet Count in PRIMA

Among patients who received ZELENA with the dose based on weight and platelet count, the median treatment duration was 11 months (range 1 day to 16 months).

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

<table>
<thead>
<tr>
<th></th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELENA N=169</td>
<td>Placebo N=244</td>
<td>ZELENA N=169</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81%</td>
<td>70%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>65%</td>
<td>37%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>57%</td>
<td>26%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>16%</td>
<td>35%</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>52%</td>
<td>13%</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>14%</td>
<td>36%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>35%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELENA monotherapy 300 mg once daily has been studied in 167 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%).

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

<table>
<thead>
<tr>
<th></th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELENA N=169</td>
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<td>Increased glucose</td>
<td>16%</td>
<td>35%</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>52%</td>
<td>13%</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>14%</td>
<td>36%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>35%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Increased aminotransferase 21% 15% 2% 0%

Table 5: Adverse Reactions Reported in ≥15% of Patients Receiving ZELENA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th></th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELENA N=169</td>
<td>Placebo N=244</td>
<td>ZELENA N=169</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81%</td>
<td>70%</td>
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<tr>
<td>Decreased platelets</td>
<td>65%</td>
<td>37%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>57%</td>
<td>26%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>16%</td>
<td>35%</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>52%</td>
<td>13%</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>14%</td>
<td>36%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>35%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELENA monotherapy 300 mg once daily has been studied in 167 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%).

Table 6: Laboratory Findings in ≥25% of All Patients Receiving ZELENA in NOVA

<table>
<thead>
<tr>
<th></th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELENA N=169</td>
<td>Placebo N=244</td>
<td>ZELENA N=169</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81%</td>
<td>70%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>65%</td>
<td>37%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>57%</td>
<td>26%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>16%</td>
<td>35%</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>52%</td>
<td>13%</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>14%</td>
<td>36%</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>35%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELENA monotherapy 300 mg once daily has been studied in 167 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%).
alkaline phosphatase increased, weight decreased, depression, episistis.

Treatment of Advanced Ovarian Cancer After Three or More Chemoheritages

The safety of ZEJULA monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 485 patients with recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall survival treatment was 3 months (range: 0.03 to 12 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

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

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

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

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (49%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=663</td>
<td>N=663</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemiaa</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></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>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td><strong>Infectious and Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

---

**CIAE—Common Terminology Criteria for Adverse Events version 4.02**

*Aemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normocytic-normochromic anemia.

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

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

Based on animal studies, ZEJULA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (3.1) of full prescribing information).

### 6.5 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 ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals may be expected.

### 6.6 Renal Impairment

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

### 6.7 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 ZEJULA in patients with moderate to severe hepatic impairment is unknown.

### 10. OVERDOSE

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

### 17. PATIENT COUNSELING INFORMATION

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

**MED-US:

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

**Bone Marrow Suppression

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

**Cardiovascular Effects

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

**Dosing Instructions

Inform patients on how to take ZEJULA (see Dosage and Administration (2.2) of full prescribing information). ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA, to not 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. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

**Embryo-Fetal Toxicity

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

**Contraception

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

**Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose (see Use in Specific Populations (8.3)).

**Trademarks

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**FDA DIGEST**

**Nivolumab/Ipilimumab Moves Into First Line for Malignant Mesothelioma**

Nivolumab (Opdivo) is approved in combination with ipilimumab (Yervoy) for the frontline treatment of adults with unresectable malignant pleural mesothelioma. The decision, which allows for nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks, is based on findings from prespecified interim analysis of the phase 3 CheckMate 743 trial (NCT02899299).

Results showed that at a minimum follow-up of 22.1 months, the combination led to superior median overall survival (OS) compared with the platinum-based standard-of-care chemotherapy (HR, 0.74; 95% CI, 0.61-0.89; P = .002). Specifically, the median OS was 18.1 months (95% CI, 16.8-21.5) with nivolumab plus ipilimumab versus 14.1 months with pemetrexed plus cisplatin or carboplatin. The 2-year OS rate also favored the immunotherapy doublet (41% vs 27%).

Malignant pleural mesothelioma is a rare cancer with limited treatment options, and when diagnosed at advanced stages, the 5-year survival rate is approximately 10%.


**FDA Awards Crizotinib Priority Review for Pediatric ALC**

Crizotinib (Xalkori) is under consideration for the treatment of pediatric patients with ALK-positive relapsed/refractory (R/R) systemic anaplastic large cell lymphoma (ALCL). The FDA is expected to make a decision on the agent’s supplemental new drug application in this setting by January 2021.

Crizotinib’s regulatory filing is based on data from the phase 1 Study A8081013 (NCT01121588) and phase 1/2 Study ADVL0912 (NCT00939770) investigations, which demonstrated encouraging antitumor activity with the kinase inhibitor in pediatric and adult patients with R/R ALCL. Study A8081013 enrolled 44 patients, 18 of whom had lymphoma. Of these, 8 achieved a complete response (CR) with crizotinib. Investigators additionally observed 1 partial response and a 2-year progression-free survival rate of 63% in this subset.

Study ADVL0912 enrolled 26 patients with R/R ALK-positive ALCL who received crizotinib at either 165 or 280 mg/m². The overall response rate with the lower dose was 83%, with 5 of 6 patients achieving a CR. Patients treated with the higher dose had an overall response rate of 90%, with 16 of 20 patients reaching CR. Partial responses were reported in 2 patients.


**Melphalan Flufenamide Undergoes Review for Triple-Class Refractory Myeloma**

Melphalan flufenamide (Melflufen), a first-in-class peptide-drug conjugate that targets aminopeptidases, received a priority review for use with dexamethasone in adults with multiple myeloma whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 anti-CD38 monoclonal antibody. The FDA is expected to issue a decision on this indication by February 28, 2021.

The new drug application is based on data from the pivotal phase 2 HORIZON trial (NCT02963493), which demonstrated an overall response rate (ORR) of 26% (95% CI, 18%-35%) in the 119 patients with triple-class refractory disease. Results from HORIZON presented during the 2020 European Hematology Association Annual Congress showed that in the intention-to-treat population (n = 157), the ORR was 29% (95% CI, 22%-37%). In the 55 patients with extramedullary disease, the ORR was 24% (95% CI, 13%-37%).

The safety of melphalan flufenamide will be further evaluated in combination with dexamethasone in the sEAport trial (NCT04534322), an expanded access program that will provide early access for patients with triple-class refractory multiple myeloma in medical need.


**Oral Paclitaxel, Encequidar Combination Is Considered for Breast Cancer**

The FDA is reviewing a regulatory filing for oral paclitaxel and encequidar (oral paclitaxel; formerly HMA30181A) in patients with metastatic breast cancer. The new drug application for the regimen received a priority review, with a decision due by February 28, 2021.

The application is based on findings from a phase 3 study (NCT02594371), which showed that the combination led to a statistically significant overall response rate (36%) compared with intravenous (IV) paclitaxel alone (24%) in this population, causing the trial to meet its primary end point (P = .01). Additionally, the rate of patients who responded to treatment and experienced a duration of response of 150 days or more was 2.5 times greater in the experimental arm versus the control arm.

At the July 25, 2019, cutoff date, results also trends toward a progression-free survival advantage and an overall survival benefit with the investigational regimen compared with IV paclitaxel (P = .077; P = .11). The study enrolled 402 patients with metastatic breast cancer who were randomized 2:1 to receive the encequidar-containing regimen (n = 265) or IV paclitaxel (n = 137).

If approved, oral paclitaxel and encequidar could offer patients with metastatic breast cancer an alternative to IV infusions, reducing patient time spent in the clinic or infusion center.


**Idecabtagene Vicleucel Moves Toward Indication in Multiple Myeloma**

Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-directed chimeric antigen receptor T-cell immunotherapy, received a priority review for adults with multiple myeloma who have been treated with at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody. The FDA is scheduled to decide on the agent’s proposed indication by March 27, 2021.

Data from the phase 2 KarMMa trial (NCT03361748) provided the basis for the biologics license application (BLA) and indicated that the product elicited a response in nearly three-fourths of patients with heavily pretreated relapsed/refractory multiple myeloma. Results presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program showed that the overall response rate with ide-cel was 73% (95% CI, 24.7-40.9; P < .0001), which included a complete response rate of 33%, a very good partial response rate of 20%, and a partial response rate of 21%. The median duration of response was 10.7 months and the median progression-free survival was 8.8 months (95% CI, 5.6-11.6), with the survival benefit increasing with a heightened target dose.

The priority review follows a refusal to file letter, issued to Bristol Myers Squibb and bluebird bio, Inc. in May 2020. The FDA stated that additional data were needed regarding the chemistry, manufacturing, and control module of the BLA but did not request further clinical or nonclinical data.

SELPERCATINIB (RETEVMO) JOINS the ranks of therapies approved for several tumor types, with indications for patients with non–small cell lung cancer (NSCLC), medullary thyroid cancer (MTC), and other thyroid malignancies with RET alterations.

On May 8, 2020, the FDA granted the drug an accelerated approval for adults with RET fusion–positive NSCLC; and adult and pediatric patients aged 12 years and older with either advanced or metastatic RET-mutant MTC who require systemic therapy or advanced or metastatic RET-fusion–positive thyroid cancer who require systemic therapy and whose disease is refractory to radioactive iodine. The indications were based on overall response rate and response duration data from the phase 1/2 LIBRETTO-001 study (NCT03157128). The 2 confirmatory phase 3 trials—LIBRETTO-431 (NCT04194944) and LIBRETTO-531 (NCT04211337)—are currently enrolling patients.

Selpercatinib is the first therapy specifically indicated for patients with tumors that harbor RET gene alterations. On September 4, 2020, the FDA approved pralsetinib (Gavreto) for RET fusion–positive NSCLC and granted a priority review for indications in MTC and thyroid cancer.

In an interview with OncologyLive®, Todd Bauer, MD, an author on the LIBRETTO-001 study, associate director of Drug Development at Sarah Cannon Research Institute, and a medical oncologist at Tennessee Oncology, both in Nashville, discussed how the highly specific nature of selpercatinib leads to greater tolerability than multityrosine kinase inhibitors and its frontline potential.

Q What is unique about selpercatinib’s safety profile?
Selpercatinib is a tyrosine kinase inhibitor that is highly specific for RET. By being this specific, selpercatinib is not only more effective against the mutated and fused versions of RET but is also better tolerated because it is not hitting off-target kinases, leading to the adverse events that we see with so many other multitaskers and kinase inhibitors.

The patients I have treated with this drug overwhelmingly tolerate it well. First-line chemotherapy or even chemotherapeutics do not come without toxicity, and selpercatinib in general is very well tolerated, with the most common adverse events being [liver function test] abnormalities and dry mouth. Selpercatinib has a 60% to 65% response rate with low incidence of adverse events, so I would always like to try to give that before I would administer cytotoxic chemotherapy or even immunotherapy.

Q How does selpercatinib’s approval advance the treatment paradigm?
Selpercatinib could be a game changer for patients who have RET mutations. In my opinion, it is hard to imagine offering chemotherapy up front with these data, so I think it could very well be a first-line therapy. And hopefully as patients and physicians learn more about selpercatinib, they will start to think about using it up front.

Selpercatinib could also be a rescue medicine for patients with thyroid cancer who had prior cabozantinib or vandetanib, and I think it will be interesting to see if we are able to translate its efficacy against RET fusions or mutations in other tumor types as well. Could this be an agent that could have greater efficacy against other diseases based purely on the presence of a RET alteration?

Selpercatinib represents the ongoing evolution of how we treat cancers, changing from treating a cancer by where it started to treating cancer by why it started. Developing therapies for individual patients rather than for a specific tissue type represents yet another step in the process of the evolution of personalized medicine that is allowing us to more effectively treat well-tolerated medicines that can manage the disease for months to years, which offers great hope for patients, for families, and for caregivers.

Q Please describe the efficacy data that led to the approval.
We saw pretty impressive response rates across the 3 patient populations in the study, with an overall response rate of 64% in the pretreated non–small cell lung cancer population with RET fusions. In the treatment-naïve RET fusion–positive group, there was an 85% response rate, meaning selpercatinib would be a great substitution for chemotherapy for these patients.

In patients with [previously treated] RET-mutant medullary thyroid cancer, we saw an overall response rate of 69%. These patients had previously been treated with standard-of-care cabozantinib [Cabometyx] or vandetanib [Caprelsa]. Keeping in mind that cabozantinib and vandetanib are similar types of multityrosine kinase inhibitors that target RET to some extent, a 69% response rate in patients who had those agents before speaks to the specificity and efficacy with which selpercatinib targets RET fusions. In treatment-naïve patients with RET-mutant medullary thyroid cancer, we saw a 73% response rate.

Most impressively, in RET fusion–positive thyroid cancer, previously treated patients showed a 79% response rate, but in treatment-naïve patients, all 8 patients had at least a partial response.

Equally important is the duration of response. In the previously treated patients with lung cancer, it was 17.5 months and more than 81% had responses that lasted for more than 6 months, so the benefit was durable. In the treatment-naïve lung cancer population, 58% had a response for more than 6 months, and we have not yet reached the median duration of response in that population.

In RET-mutant medullary thyroid cancer, 76% and 61% of pretreated patients and treatment-naïve patients [respectively] had a response that endured for more than 6 months. In the treatment-naïve group, the median duration of response was 22 months. Similar numbers were seen in RET fusion–positive thyroid cancer: a median duration of response in a previously treated group of 18.4 months with 87% lasting more than 6 months.

REFERENCES
### FDA approval—May 8, 2020

FDA grants accelerated approval for the kinase inhibitor selpercatinib (Retevmo) for adults with RET fusion–positive non–small cell lung cancer (NSCLC) and adult and pediatric patients aged 12 years and older with either advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy or advanced or metastatic RET fusion–positive thyroid cancer who require systemic therapy and whose disease is refractory to radioactive iodine.

**Mechanism of action:**
- Selpercatinib inhibits wild-type RET and several mutated RET isoforms as well as VEGFR1 and VEGFR3 with $IC_{50}$ values from 0.92 nM to 67.8 nM.

**How supplied:**
- 40- and 80-mg capsules

**Company:** Eli Lilly and Company

### PIVOTAL CLINICAL TRIAL

LIBRETTO-001 (NCT03157128) is a multicenter, multicohort trial that enrolled 105 patients with RET fusion–positive NSCLC who were previously treated with cabozantinib (Cabometyx) or vandetanib (Caprelsa) and 88 patients who were treatment-naïve; and 27 patients with RET fusion–positive thyroid cancer whose disease was refractory to radioactive iodine, 8 of whom had not received prior systemic therapy.

### EFFICACY RESULTS IN THE LIBRETTO-001 TRIAL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR (%)</th>
<th>DOR, months (95% CI)</th>
<th>Patients with response lasting ≥ 6 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic RET fusion+ NSCLC (n = 39)</td>
<td>85% (70%-94%)</td>
<td>NE (12.0-NE)</td>
<td>58%</td>
</tr>
<tr>
<td>RET-mutant MTC (n = 88)*</td>
<td>73% (62%-82%)</td>
<td>11.0% 61%</td>
<td>22.0 (NE-NE)</td>
</tr>
<tr>
<td>RET fusion+ thyroid cancer (n = 8)*</td>
<td>100% (63%-100%)</td>
<td>12.5% 88%</td>
<td>NE (NE-NE)</td>
</tr>
</tbody>
</table>

### BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve RET-mutant MTC (n = 88)</td>
</tr>
<tr>
<td>Previously treated RET fusion+ NSCLC (n = 105)</td>
</tr>
<tr>
<td>Previously treated RET fusion+ NSCLC (n = 88)</td>
</tr>
<tr>
<td>Treatment-naïve RET fusion+ NSCLC (n = 27)</td>
</tr>
</tbody>
</table>

### WARNINGS AND PRECAUTIONS

- Hepatotoxicity
- Hypertension
- QT interval prolongation
- Hemorrhagic events
- Hypersensitivity
- Risk of impaired wound healing
- Embryo-fetal toxicity

### COMMON ADVERSE EFFECTS

The most common adverse reactions (>20%) were dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation, headache, nausea, and abdominal pain.

### REFERENCE

INTERACTIVE NEWS
A selection of exclusive articles and videos available on OncLive.com and other MJH Life Sciences™ websites.

TOP TWEETS
@OncLive
FDA Grants Breakthrough Therapy Designation to Magrolimab for #MDS @US_FDA
https://bit.ly/2RAe5pe

@OncLive
As the impact of the #COVID-19 pandemic lingers into the later part of 2020, consideration is needed regarding the lasting effects on patients with cancer who may have experienced delayed care or diagnosis. @CHULiege @myESMO #ESMO2020 #coronavirus

@OncLive
Focal Ultrasound Ablation Demonstrates Utility as Primary Therapy in Prostate Cancer @ALDCAbreu @KeckMedUSC #pcsm
https://bit.ly/33z5QiO

@OncLive
The first patient has been enrolled on the phase 2 portion of the LIO-1 trial, which will examine the combination of lucatinib plus nivolumab in those with gynecologic cancers. @ErikaHamilton9 @SarahCannonDocs #gynca

RESEARCH REFLECTIONS
@OncLive
HAMD HOMES IN ON KEY EFFORTS MADE IN MELANOMA
Review key abstracts in melanoma presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program with Omid Hamid, MD, as he discusses findings related to the optimal duration and sequencing of checkpoint inhibitors, adoptive cell therapy options, and subgroups of patients with mucosal melanoma and brain metastases.

TALKING TUMORS
Sara M. Tolaney, MD, MPH, discusses the use of neoadjuvant and adjuvant HER2-directed therapies in early-stage HER2-positive breast cancer and shares insights on how risk status is being used to tailor targeted agents to these patients, key trials focused on delineating optimal deescalated and escalated treatment strategies, and ongoing research in the HER2-low setting.
LISTEN: https://bit.ly/2RuvSO4

FDA APPROVAL INSIGHTS
@OncLive
Shilpa Gupta, MD, addresses the June 30, 2020, approval of avelumab (Bavencio) as a maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-based chemotherapy. The regulatory decision was based on findings from the phase 3 JAVELIN Bladder 100 trial (NCT02603432).
LISTEN: https://bit.ly/3mqh6Xi

MARVELS IN MEDICINE
Veda N. Giri, MD, and Leonard G. Gomella, MD, delineate the first multidisciplinary, consensus-driven framework for genetic testing in prostate cancer, borne out of Philadelphia Prostate Cancer Consensus Conference 2019. Giri, lead author of the guidelines, and Gomella detail key aspects of the recommendations that could have clinical implications for men in this space.

RAPID READOUT
Zev A. Wainberg, MD, reviews long-term follow-up data from the phase 1/2 study (NCT02551991) of liposomal irinotecan, 5-fluorouracil, leucovorin, and oxaliplatin in patients with pancreatic ductal adenocarcinoma (PDAC). Results showed that the 4-drug combination, known as NALIRIFOX, is tolerable for patients with treatment-naive locally advanced or metastatic PDAC. NALIRIFOX is being evaluated in the ongoing phase 3 NAPOLI 3 trial (NCT04083235).
WATCH: https://bit.ly/2ZO1C5P

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For adults with intermediate- or high-risk myelofibrosis (MF)¹

INTERVENE WITH

JAKAFI® (RUXOLITINIB)

AT DIAGNOSIS

**Indications and Usage**

Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

**Important Safety Information**

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 × 10⁹/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leuкоencephalopathy (PML) has occurred with Jakafi. While tapering Jakafi, evaluate and treat any intercurrent illness and consider gradual tapering rather than abrupt discontinuation or discontinue Jakafi without consulting their physician. When discontinuing or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt treatment

**SIGNIFICANTLY MORE PATIENTS RECEIVING JAKAFI EXPERIENCED IMPROVEMENT IN MF-RELATED SPLENOMEGALY¹,³,⁵**

**COMFORT-I PRIMARY ENDPOINT¹,³,⁵**

<table>
<thead>
<tr>
<th>of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24</th>
<th>vs</th>
<th>0.7% of patients receiving placebo (P &lt; 0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.4 years median duration of spleen response among primary responders (n = 65)⁴

**COMFORT-II PRIMARY ENDPOINT¹,⁵,¹¹**

<table>
<thead>
<tr>
<th>of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 48</th>
<th>vs</th>
<th>0% of patients receiving best available therapy¹ (P &lt; 0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹In patients who are not transplant candidates.
²Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate risk based on MIPSS-70 (threshold of ≤3 prognostic variable points), and very low, low, or intermediate risk based on MIPSS-70+ (version 2.0; threshold of ≤3 prognostic variable points).²
³Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate risk based on MIPSS-70 (threshold of ≤3 prognostic variable points), and very low, low, or intermediate risk based on MIPSS-70+ (version 2.0; threshold of ≤3 prognostic variable points).²

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The NCCN Guidelines® are evidence-based guidelines intended to aid physicians in making treatment decisions for their patients. The NCCN Guidelines are not a treatment plan for patients. Physicians must use their best judgment and consider other circumstances in each individual case. To learn more about Jakafi, visit JAKAFI.com. Jakafi and the Jakafi logo are registered trademarks of Incyte.

To learn more about Jakafi, visit JAKAFI.com.
Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF),

Indications and Usage

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.

Manage thrombocytopenia by reducing the dose or temporarily interrupting treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 and neutropenia, which are each dose-related effects. Perform a withholding Jakafi until recovery promptly. Use active surveillance and prophylactic antibiotics according to patients receiving Jakafi for signs and symptoms of infection and manage

COMFORT-II PRIMARY ENDPOINT1,5 II

EXPERIENCED IMPROVEMENT IN MF-RELATED SPLENOMEGALY 1,3,5

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.2

†Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate

‡ In patients who are not transplant candidates.

4.4 years median duration of spleen response among primary responders (n = 65)§

Ruxolitinib (Jakafi) is a Category 2A* treatment option for both symptomatic

WITH

VS

JAKAFI 3-YEAR AND 5-YEAR OVERALL SURVIVAL ANALYSES

For adults with intermediate- or high-risk myelofibrosis (MF)1

of patients receiving

achieved a ≥35% reduction in

Increases in hepatitis B viral load with or without associated elevations

Progressive multifocal leukoencephalopathy (PML) has occurred with

Tuberculosis (TB) infection has been reported. Observe patients taking

be based on the overall risk-benefit determination

or interrupting Jakafi, evaluate and treat any intercurrent illness and consider

or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations

Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for hyperlipidemia

In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections

Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy

Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

P

0%

VS

JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 51%

All patients in the placebo group either crossed over to Jakafi at a median of 9 months or discontinued

The 5-year overall survival analysis is not included in the Full Prescribing Information for Jakafi. Although the 3-year overall survival analysis is presented in the Full Prescribing Information, P values and hazard ratios are omitted from the overall survival Kaplan-Meier curves.

COMFORT-I was not designed to compare survival probabilities between Jakafi and placebo at 3 or 5 years.

Patients randomized to placebo were eligible to cross over to receive Jakafi because of progression-driven events or at the physician’s discretion; however, these patients continued to be grouped within their original randomized assignment for analysis purposes.

COMFORT-I (Controlled Myelofibrosis study with Oral Jak inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 303 patients in intermediate-2- or high-risk MF. The primary endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.7

Duration of spleen response was defined as the interval between the first spleen response measurement that was ≥35% reduction from baseline and the data of the first measurement that was no longer a ≥35% reduction from baseline that was also a ≥25% increase from nadir.

COMFORT-II: 5-YEAR ANALYSIS OF JAKAFI AND BEST AVAILABLE THERAPY

At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy

Overall survival was a prespecified secondary endpoint in COMFORT-II

JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 56%

All patients in the best available therapy group either crossed over to Jakafi at a median of 17 months or discontinued

BAT, best available therapy.

The 5-year overall survival analysis is not included in the Full Prescribing Information for Jakafi. Although the 3-year overall survival analysis is presented in the Full Prescribing Information, P values and hazard ratios are omitted from the overall survival Kaplan-Meier curves.

COMFORT-II was not designed to compare survival probabilities between Jakafi and best available therapy at 3 or 5 years.

Patients randomized to best available therapy were eligible to cross over to receive Jakafi because of progression-driven events or at the physician’s discretion; however, these patients continued to be grouped within their original randomized assignment for analysis purposes.

COMFORT-II (Controlled Myelofibrosis study with Oral Jak inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2- or high-risk MF. The primary endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI.7

Best available therapy in COMFORT-II included hydroxyurea (46.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thio guanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, ace tysalicylic acid, cytarabine, and cidofovir.5

For more data on long-term results with Jakafi, visit JakafiResults.com

To learn more about Jakafi, visit HCP.Jakafi.com.

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

BRIEF SUMMARY: For full prescribing information, see package insert.

INDICATIONS AND USAGE Myelofibrosis: Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.

Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Dosage and Administration (2.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2.2), and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 x 10^9/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Perform complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2.2) and Adverse Reactions (6.1) in Full Prescribing Information].

Risk of Infection Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly.

Use active surveillance and prophylactic antibiotics according to clinical guidelines. Tuberculosis Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior history of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate duration of treatment with a drug effective against tuberculosis was not observed. Clinical studies of Jakafi in patients with active or latent tuberculosis where an adequate duration of treatment with a drug effective against tuberculosis was not observed.

In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi. Mean decreases in hemoglobin reached a nadir of 0.95 g/dL and 0.65 g/dL at the maximum recommended dose of 25 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 x 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 x 10^9/L), 15% and 25% of patients, respectively, required a dose reduction below the pretreatment level, for the duration of the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2].

Thrombocytopenia, anemia and neutropenia are dose-related effects.

The most common nonhematologic adverse reactions were bruising, dizziness and headache [see Table 3]. Table 3 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=150)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Bruising</td>
<td>23</td>
<td>1 &lt; 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0 &lt; 1</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0 &lt; 1</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>9</td>
<td>0 &lt; 1</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>1 &lt; 1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0 &lt; 1</td>
</tr>
</tbody>
</table>

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

Includes concomitant use of cyclophosphamide, etoposide, irinotecan, methotrexate, or other chemotherapy regimens.

In a single-arm, open-label study, 110 patients with relapsed or refractory acute myeloid leukemia, acute myeloid leukemia, or myelodysplastic syndrome treated with Jakafi had a decrease in platelet transfusion requirements. Compared to patients treated with placebo, patients treated with Jakafi had a 60% decrease in the number of platelet transfusions required at 12 weeks.

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U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 9669376; 9814722; 10016429

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=150)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>96</td>
<td>34</td>
</tr>
<tr>
<td>Platelet</td>
<td>98</td>
<td>35</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline

National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-Controlled Study

- 25% of patients experienced a 20% decrease in platelet count with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was 1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol.

The incidence of Grade 2 cholesterol elevations was 1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Clinical Trial Experience in Polycythemia Vera: In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see Clinical Studies (7.4.2) in Full Prescribing Information]. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 52.

Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥5% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 52 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=110)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Harpep Zoster</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 continued above.
Infection and monitor CBCs every 2 to 4 weeks until doses are stabilized, and Jakafi until recovery in infections taking Jakafi. The effect of Jakafi on viral replication in seeking treatment as early as possible if suspected patients about early signs and symptoms of herpes zoster and to Jakafi is indicated for treatment of steroid-refractory chronic HBV infection should be treated and monitored according in the treatment of tuberculosis before starting Jakafi. The decision reported in patients receiving Jakafi. Observe patients receiving clinical guidelines.

Jakafi is a registered trademark of Incyte. All rights reserved. U.S. Patent Nos. 7,958,957; 8,153,682; 8,272,883; 8,242,481; 8,650,613; 8,897,912; 9,147,722; 10,016,429 © 2011-2020 Incyte Corporation. All rights reserved. Revised August 2020 PLL-JNK-00049
COVID-19 Crisis Increases Risk of Distress, Burnout Among Oncology Professionals

by KRISTI ROSA

EMERGING DATA DEMONSTRATE the significant effect the coronavirus disease 2019 (COVID-19) pandemic has had on oncology providers’ job performance and well-being. To examine and address how COVID-19 has affected health care providers (HCPs), the European Society for Medical Oncology (ESMO) Resilience Task Force launched a series of surveys to assess the virus’ effect on current daily practice, physician well-being and burnout, and the support available to address these challenges.¹,²

“This is the largest COVID-19 survey series [that has been conducted] for oncology professionals. Well-being and job performance varied between countries and were related to COVID-19 crude mortality rate,” said Susana Banerjee MBBS, MA, PhD, FRCP, as part of a presentation at the ESMO Virtual Congress 2020. “COVID-19 is impacting well-being, burnout, and job performance, and main predictors include resilience and change to work hours. Risk of distress and burnout has increased, while job performance has improved during the pandemic. Urgent measures to address well-being are essential.”

The surveys were disseminated online via email and social media, as well as through the OncoAlert network, according to Banerjee. The focus of the first survey, which took place from April 16 through May 3, 2020, was to learn more about how the pandemic has affected the roles of HCPs in the space, how cancer care has changed in light of new information, how these changes are affecting well-being, and the resources available to HCPs. The second survey, which was conducted from July 16 through August 5, focused on the longer-term impact of the pandemic and other sequelae such as burnout and job performance.

SURVEY 1 SHOWS HIGH DISTRESS, POOR WELL-BEING

A total of 1520 participants from 101 countries responded to the first survey. Two-thirds of responses were from Europe, 45% of participants were younger than 40 years, 51% were female, and the majority (71%) of respondents were White. Moreover, 70% were medical oncologists and 22% were trainees. Notably, 67% of participants reported changes in professional duties since the start of the COVID-19 pandemic, and 78% reported increased concern for their personal safety at work.

On April 24, investigators obtained the COVID-19 crude mortality rate according to country. “As mortality increases, [there is] higher distress and poorer well-being,” said Banerjee, a consultant medical oncologist and clinical research lead for the Gynaecology Unit at The Royal Marsden in London, United Kingdom, and chair of the ESMO Resilience Task Force.

The ESMO Resilience Task Force also conducted several analyses to further examine the association between the pandemic and factors beyond crude mortality rate.

Results showed that participants who felt valued by their organization indicated that their working conditions were “pleasant” and reported higher levels of perceived resilience compared with other respondents who had lower distress and thus better wellbeing. “Psychological resiliency was shown throughout to be a factor predicting well-being, burnout, and performance levels,” noted Banerjee. Additional indicators of better well-being/low distress included age greater than 40 years and male sex (TABLE).¹

Participants who reported an increase in working hours and concerns about the impact of the virus on their training/career, had self-isolated because of symptoms, had reduced clinical trial activity, experienced changes in diet, avoided thinking about well-being/distress, and/or talked to colleagues to seek emotional support were all at increased risk of distress.
The likelihood of burnout was also higher among those who reported increased work hours with more after-hours work and/or concerns regarding their training. Adequate job control was associated with improved job performance since the start of the pandemic.

**SURVEY 2 REPORTS BURNOUT SPIKES**
A total of 942 HCPs responded to the second survey. Three months later, the reported risk of distress was higher compared with what was observed in the first survey, translating to elevated rates of worse well-being (25% vs 33%; emotional Well-Being Index ≥ 4; P < .0001). More participants in survey 2 than in survey 1 reported feeling burned out, at 49% and 38%, respectively (P < .0001). Job performance trended toward improvement. Despite burnout rates, improved job performance rose from 34% at the start of the pandemic to 51% in survey 2 (score < 3.5; P < .0001).

The ESMO Resilience Task Force also asked respondents what would be most helpful for them or their colleagues moving forward. The majority of participants (86%) said flexible working hours, including the ability to work from home, would be most helpful. The results affirm what HCPs in the oncology space are evidently well aware of: “COVID-19 has changed our world,” Banerjee said. “These changes include patient management plans, the way we deliver care, [and] our daily working practice, taken together with our personal situations outside work. The impact of COVID-19 on well-being has the potential for serious negative consequences on work, home life, and patient care.”

A third survey is planned for 2021, according to Banerjee, who added that the goal is to have more oncologists around the world participate so that the Resilience Task Force can more closely examine the different ways in which the COVID-19 pandemic is affecting HCPs in each country.

“The ESMO Resilience Task Force will be looking into furthering specific interventions so that we can continue to further help and support [oncology professionals] during the pandemic and, importantly, beyond,” Banerjee concluded.

**REFERENCES**

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**TABLE. Predictors of Well-being, Burnout, and Job Performance**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Negative variable</th>
<th>Positive variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-being (better well-being/low distress)</td>
<td>• Concern about well-being or training/career</td>
<td>• Resilience</td>
</tr>
<tr>
<td></td>
<td>• Increased work hours</td>
<td>• Valued by organization</td>
</tr>
<tr>
<td></td>
<td>• Self-isolated because of symptoms</td>
<td>• “Pleasant” working conditions</td>
</tr>
<tr>
<td></td>
<td>• Avoiding thinking about well-being</td>
<td>• Age &gt; 40 years</td>
</tr>
<tr>
<td></td>
<td>• Reduced clinical trial activity</td>
<td>• Male sex</td>
</tr>
<tr>
<td></td>
<td>• Changes in diet</td>
<td>• Change in physical activity</td>
</tr>
<tr>
<td></td>
<td>• Talking to colleagues for emotional support</td>
<td></td>
</tr>
<tr>
<td>Burnout</td>
<td>• Has seen a psychiatrist/psychologist</td>
<td>• Resilience</td>
</tr>
<tr>
<td></td>
<td>• Increased work hours</td>
<td>• Non-White ethnicity</td>
</tr>
<tr>
<td></td>
<td>• More after-hours work</td>
<td>• “Pleasant” working conditions</td>
</tr>
<tr>
<td></td>
<td>• Concern about well-being or training/career</td>
<td>• Supported by government</td>
</tr>
<tr>
<td>Job performance since start of pandemic</td>
<td>• Worried about negative impact on research</td>
<td>• Resilience</td>
</tr>
<tr>
<td></td>
<td>• Crude mortality rate</td>
<td>• Adequate job control</td>
</tr>
<tr>
<td></td>
<td>• More work-from-home hours</td>
<td>• Job in surgical oncology or hematology/oncology</td>
</tr>
<tr>
<td></td>
<td>• Distraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reduced clinical trial activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Non-White ethnicity</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE. Predictors of Well-being, Burnout, and Job Performance**

The majority of participants (86%) said flexible working hours, including the ability to work from home, would be most beneficial. Regarding other strategies, 81% cited a workshop or course on well-being, burnout, and coping mechanisms would be useful; 79% said counseling and psychological support services; and 73% identified a practical guide/handbook or self-help resource.
At the first diagnosis of a bone metastasis

Take action to reduce the risk of bone complications* with XGEVA®

XGEVA® Q4W demonstrated superior prevention of bone complications vs zoledronic acid (ZA) in patients with solid tumors

In a prespecified integrated analysis of 3 pivotal trials (N=5,723), XGEVA® prevented bone complications for a median of 27.7 months vs 19.5 months for ZA: HR\textsuperscript{1} =0.83 [95% CI: 0.76-0.90]; P<0.001\textsuperscript{2}

Study design:

Based on three phase 3, double-blind, double-dummy, active-controlled studies comparing XGEVA® with ZA for the prevention of bone complications in patients with bone metastases from solid tumors or multiple myeloma. Patients received 120 mg XGEVA® subcutaneously every 4 weeks or 4 mg ZA intravenously (IV) every 4 weeks. If the primary endpoint of noninferiority was met, the superiority test for secondary endpoints was conducted, including time to first bone complication and time to first and subsequent bone complications. Zoledronic acid 4 mg was administered as an IV infusion over a minimum of 15 minutes, once every 4 weeks, in accordance with prescribing information. Select exclusion criteria: patients with creatinine clearance <30 mL/min, patients receiving current or prior IV oral bisphosphonate therapy for bone metastases were excluded. Patients who received prior oral bisphosphonates for the treatment of osteoporosis were not excluded, as long as the treatment was stopped before the first dose of the investigational drug. Per protocol, based on the ZA label, the IV product was dose-adjusted for baseline creatinine clearance <40 mL/min. No dose adjustments were made, and redoses were withheld, for increased serum creatinine for the subcutaneous (SC) product.

Select exclusion criteria: patients with creatinine clearance <30 mL/min; patients receiving current or prior IV bisphosphonate therapy; patients receiving oral bisphosphonates for the treatment of osteoporosis were not excluded.

*Bone complications, also known as skeletal-related events (SREs), are defined as radiation to bone, pathologic fracture, surgery to bone, and spinal cord compression.\textsuperscript{1}

\textsuperscript{1}Hazard ratio (HR) is defined as the increase or decrease in likelihood of an event of interest in this case, a bone complication, for one group relative to a comparator group.

\textsuperscript{2}P value for superiority.

---

Deviation from standard XGEVA® Q4W demonstrated an increased rate of bone complications\textsuperscript{3}

- Results from a retrospective study (N=60) showed patients in the deviated interval arm (dosing once every 31 to 56 days) experienced more bone complications compared with the standard interval arm (Q4W):\textsuperscript{4}

  - Study demographics: standard interval [31% breast cancer, 34.5% prostate cancer, 6.9% lung cancer]; deviated interval [41.9% breast cancer, 16.1% prostate cancer, 19.4% lung cancer]

<table>
<thead>
<tr>
<th>Standard interval</th>
<th>Deviated interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of bone complications (N=29)</td>
<td>31%</td>
</tr>
<tr>
<td>Incidence of bone complications (N=31)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{3}Dosing was considered once every 27-50 days in this study.

\textsuperscript{4}A retrospective case cohort study of sixty patients treated from 2012 to 2015 at a single cancer center: Subjects must have received two or more doses.

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Indication

XGEVA® is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.

Important Safety Information

Hypocalcemia

- Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Concomitant use of calcimimetics and other drugs that can lower calcium levels may worsen hypocalcemia risk and serum calcium should be closely monitored. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.

- An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction [creatinine clearance less than 30 mL/minute and/or on dialysis], and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Please see additional Important Safety Information on next page.
Important Safety Information (cont’d)

Hypersensitivity
• XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient
• Patients receiving XGEVA® should not take Prolia® (denosumab).

Osteonecrosis of the Jaw
• Osteonecrosis of the jaw (ONJ) has been reported in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with cancer, the incidence of ONJ was higher with longer duration of exposure.
• Patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance are at a greater risk to develop ONJ. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections.
• Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®. Consider temporarily interrupting XGEVA® therapy if an invasive dental procedure must be performed.
• Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture
• Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.
• Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone (GCTB) and in Patients with Growing Skeletons
• Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in XGEVA®-treated patients with GCTB and in patients with growing skeletons within one year of treatment discontinuation. Monitor patients for signs and symptoms of hypercalcemia after treatment discontinuation and treat appropriately.

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation
• Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures. When XGEVA® treatment is discontinued, evaluate the individual patient’s risk for vertebral fractures.

Embryo-Fetal Toxicity
• XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects.
• Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Adverse Reactions
• The most common adverse reactions in patients receiving XGEVA® with bone metastases from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.
• For multiple myeloma patients receiving XGEVA®, the most common adverse reactions were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. The most common serious adverse reaction was pneumonia. The most common adverse reaction resulting in discontinuation of XGEVA® was osteonecrosis of the jaw.

Please see accompanying Prescribing Information.


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IN LESS THAN 10 YEARS, immune checkpoint inhibitors (ICIs) have dramatically altered the treatment landscape for patients with metastatic melanoma, helping to drive an improvement in 5-year survival rates from historical levels of less than 10% to more than 50% with some regimens.\(^1,2\)

Mario Sznol, MD, was drawn to cancer immunotherapy research from the beginning of his oncology career in the mid-1980s. What he finds most exciting is the way the initial breakthrough in immuno-oncology has expanded to so many other cancer indications, Sznol said in an interview with OncologyLive\(^*\). Monoclonal antibodies that target the immune checkpoint protein PD-1, or its main ligand, PD-L1, are now approved in various clinical settings for 18 tumor types plus 2 biomarker-driven indications across solid tumors (TABLE).\(^3\) Additionally, the CTLA-4 immune checkpoint inhibitor ipilimumab (Yervoy) is approved in 6 tumor types.\(^4\)

However, amid this dizzying pace of advancement, many oncologists struggle to keep up not only with developments but also with how to treat patients suffering from the array of adverse events (AEs) encountered with ICI therapy, said Sznol, professor of medicine (medical oncology) at Yale School of Medicine and coleader of the Cancer Immunology Research Program at Yale Cancer Center, both in New Haven, Connecticut. He also is president of the Society for Immunotherapy of Cancer (SITC).

Importantly, Sznol said, the risk of potentially severe AEs from ICIs or unfamiliarity with their management could influence decisions to offer or receive these agents. "Although toxicity is always an important consideration before offering a therapy, most AEs from ICIs can be managed and reversed, and in most settings, the overall benefit-to-risk ratio is very favorable," he noted.

In that regard, Sznol has helped make addressing these AEs one of the primary goals of the 5th Annual International Congress on Immunotherapies in Cancer\(^*\). The conference, hosted by Physicians’ Education Resource\(^*\), LLC (PER\(^*\)), will be held on December 12, 2020, as a live virtual meeting, with a focus on practice-changing applications. Sznol is cochairing the meeting, along with Naiyer A. Rizvi, MD, the Price Family Professor of Medicine and director of Thoracic Oncology at Columbia University Herbert Comprehensive Cancer Center in New York, New York. Rizvi is also codirector of cancer immunotherapy at Columbia University Irving Medical Center and research director of the Price Family Comprehensive Center for Chest Care at NewYork-Presbyterian Hospital.

As ICIs have become more widely used and incorporated into more combinations, physicians are more likely to encounter some of the rare and unusual AEs, said Sznol, who also is coleader of cancer immunology at Yale Cancer Center.

Dermatologic toxicities are the most frequently reported AE with ICI therapy (all grades, 30%-40% with anti–PD-1/PD-L1 agents; approximately 50% with anti–CTLA-4), particularly rash or pruritus, which has been reported in 13% to 20% of patients who receive the PD-1 inhibitors pembrolizumab (Keytruda) or nivolumab (Opdivo).\(^5\) However, although oncologists can generally manage rash without much difficulty, some skin toxicities can be very severe and other common reactions can lead to significant morbidity unless addressed.
quickly and effectively, Sznol noted. These include colitis, liver function test (LFT) abnormalities, endocrinopathies, nephritis, and pneumonitis. But toxicity can involve any organ system, so it is critical that physicians and all other health care providers involved in patient care have the confidence and skill to administer treatment, Sznol said.

“I expect that fellows who are currently being trained will be used to seeing all these events and for them, managing ICI toxicity will become second nature,” Sznol said. “But health care providers trained in the 1980s or 1990s—and the first of these agents, ipilimumab, was approved only in 2011—may be encountering a set of very unfamiliar AEs. Community oncologists are certainly capable of managing ICI toxicity and in fact manage AEs from other agents, such as chemotherapy, that could lead to even more severe complications, for example, neutropenia. It’s just a matter of developing a different set of reflexes for what to do.”

Sznol said the conference would be a venue for oncologists to learn about ICI toxicities and practical strategies for addressing them. Some of the AEs are so unusual that even physicians in major cancer centers—himself included—find themselves emailing peers across the country to try to find the best treatment option. He said conference organizers have recruited experts who truly understand the use of immunotherapy to provide state-of-the-art information.

“These drugs have been out there for 6 or 7 years, but it’s not surprising that there’s still some uncertainty about how to treat AEs in the clinic, even within very experienced academic centers,” Sznol said. “And perhaps as physicians and their staff are gaining experience, management of some AEs may differ from more established algorithms. The major clinical questions usually revolve around when to start steroids, the initial dose of steroids, when and how to taper the steroids, when to move to a second immunosuppressive agent, or when one can consider restarting ICI treatment after resolution of toxicity.”

Sznol said continuing education is helpful for clinical management of patients whose severe AEs do not respond to initial high-dose steroids and may require a second immunosuppressive agent, most often for colitis or LFT abnormalities. For colitis, oncologists may not be comfortable with prescribing a tumor necrosis factor inhibitor, generally infliximab (Remicade), or a third-line anti-inflammatory agent, if necessary, such as vedolizumab (Entyvio), or, in the case of LFT elevations, mycophenolate. Continuing education is also helpful in the recognition and initial management of rare ICI-related toxicities such as myositis and myocarditis, as well as neurologic and hematologic events.

Jeffrey S. Weber, MD, PhD, a 2016 Giants of Cancer Care® award winner who is giving a presentation at the PER® conference about toxicity management that will focus on patient cases, agreed that more education is needed, particularly for emergency room (ER) physicians.

“The classic situation is ER docs who are not used to seeing these patients and don’t think about immune toxicity,” said Weber, deputy director of the Perlmutter Cancer Center and codirector of the melanoma research program at NYU Langone Health in New York, New York. “They’ll think there’s some other cause and not give steroids. The patients will end up going home and coming right back. It’s taking a significant effort with [ED] docs, including giving in-services, just to raise the consciousness of what immune toxicity is about.”

Weber said an issue that has arisen this year involves ensuring that ER physicians are aware that pneumonitis can be a toxicity associated with immunotherapy. The concern is that physicians will assume the condition is related to coronavirus disease 2019. “The solution is increased education and having a cohort of experts who know the immunotherapy business or a cadre of consultants in endocrinology, gastroenterology, and pulmonology who can see the patients quickly,” he said.

### TABLE. Clinical Settings for FDA-Approved PD-1/PD-L1 Inhibitors

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>Approved immune checkpoint inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple-negative breast cancer</td>
<td>●</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>●</td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td>● ●</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td>●</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>●</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>●●</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>●</td>
</tr>
<tr>
<td>Head and neck squamous cell carcinoma</td>
<td>●</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>●</td>
</tr>
<tr>
<td>Malignant pleural mesothelioma</td>
<td>●</td>
</tr>
<tr>
<td>Melanoma</td>
<td>●</td>
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<tr>
<td>Merkel cell carcinoma</td>
<td>●●</td>
</tr>
<tr>
<td>MSI-H/dMMR colorectal cancer</td>
<td>●</td>
</tr>
<tr>
<td>MSI-H/dMMR solid tumors</td>
<td>●</td>
</tr>
<tr>
<td>Non–small cell lung cancer</td>
<td>● ● ●●</td>
</tr>
<tr>
<td>Primary mediastinal large B-Cell Lymphoma</td>
<td>●</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>●●</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>● ●●</td>
</tr>
<tr>
<td>TMB-high solid tumors</td>
<td>●</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>●●●●</td>
</tr>
</tbody>
</table>

**dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; TMB, tumor mutational burden.**

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>Approved immune checkpoint inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>●</td>
</tr>
<tr>
<td>Avelumab (Bavencio)</td>
<td>●</td>
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<tr>
<td>Pembrolizumab (Keytruda)</td>
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<tr>
<td>Durvalumab (Imfinzi)</td>
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<tr>
<td>Nivolumab (Opdivo)</td>
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<tr>
<td>Pembrolizumab (Keytruda)</td>
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<tr>
<td>Merckel cell carcinoma</td>
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<td>MSI-H/dMMR colorectal cancer</td>
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<td>MSI-H/dMMR solid tumors</td>
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</tr>
<tr>
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<td>Primary mediastinal large B-Cell Lymphoma</td>
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</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>●●●●</td>
</tr>
</tbody>
</table>

**CHECKPOINT LANDSCAPE**

The concept of using immunotherapy against cancer was born in 1891 when William B. Coley, MD, a renowned surgeon at Memorial Hospital in New York, used bacteria to successfully treat a New York City man with many inoperable advanced tumors.
A century later, the field had seen few advances. In 2002, when it came to treating patients with metastatic melanoma, 2 immunotherapeutic options were available: interferon alpha and IL-2. High doses of IL-2 “cured” somewhere between 5% and 10% of patients with metastatic melanoma,” Sznol said. “And with chemotherapy, we cured almost no one. For chemotherapy, the response rates were in the 15% to 20% range, and [the responses] didn’t last very long.”

It was the excitement around the potential for immunotherapeutic approaches that changed Sznol’s career path. In the mid-1980s, he was participating in a fellowship at The Mount Sinai Hospital in New York, New York, which was among the few institutions studying IL-2. “That was my very first exposure to immune therapies,” Sznol said. “And the science was really fascinating.”

IL-2 stayed on Sznol’s radar when he took a job at the National Cancer Institute (NCI) in Bethesda, Maryland, in the Cancer Therapy Evaluation Program (CTEP), where he remained for 12 years. His role was to oversee the development of immunotherapy portfolios.

“We got to see everything then—interleukin-2, all the different cytokines that were developed, all kinds of cancer vaccines, and cell therapies,” Sznol said. “We acted like a drug company. One of CTEP’s roles was to develop investigational agents for cancer. So I got a huge amount of exposure to these immunotherapeutic agents. But when I left in ’99, I was not so optimistic about the agents then in development. I left the NCI and went to a biotech company to do something very different although still related to immunotherapy.”

While working at Vion Pharmaceuticals, Sznol and colleagues attempted to target tumors with modified Salmonella, a strategy he initially brought for collaborative study with former colleagues at the NCI. They found that in mouse tumor models, the bacteria could replicate preferentially in the tumor microenvironment, and they hoped to be able to deliver cytokines and chemokines there. However, the initial human trials were unable to reproduce the murine results. At that point, Sznol returned to academia, in time for early research into anti-CTLA-4 and anti-PD-1 drugs, which, because of their activity in patients, “just made life much better,” he said. The experiences and the bounty of possibilities helped him envision the future.

“We’ve always been very interested in immunotherapy for cancer, and at Yale I focused on melanoma and renal cancer together with my colleague Harriet Kluger, MD,” Sznol said. “Our center [at Yale] was the first to give the nivolumab-ipilimumab combination to a patient; we conducted the initial part of that phase 1 trial together with Jedd D. Wolchok, MD, PhD, and his colleagues at Memorial Sloan Kettering [MSK] beginning in December 2009. It was a wonderful collaboration between our centers and Medarex/Bristol Myers Squibb, and the results that we saw in that trial were remarkable.”

During a career that has spanned more than 30 years, Sznol has been involved in the development of many immune-modulating therapies, particularly for melanoma and renal cell carcinoma (RCC). Notably, he was among the key investigators in the first multidose phase 1 study of nivolumab (NCT00730639), which demonstrated responses in patients with melanoma, non-small cell lung cancer (NSCLC), and RCC, according to findings reported in the New England Journal of Medicine in 2012.8

In 2013, the results from the first dual ICI therapy with nivolumab and ipilimumab were reported. The combination elicited an objective response rate of 40% (95% CI, 27%-55%) among 52 evaluable patients with unresectable stage III or IV melanoma treated concurrently across all dose levels in the phase I CA209-004 trial (NCT01024231).9

Today, the combination of nivolumab plus ipilimumab is approved for unresectable or metastatic melanoma; as first-line treatment for metastatic PD-L1-positive (≥ 1%) NSCLC without EGFR or ALK mutations or in combination with chemotherapy for metastatic or recurrent NSCLC without those mutations; hepatocellular carcinoma (HCC) previously treated with sorafenib ( Nexavar); microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) metastatic colorectal cancer progressing after chemotherapy; intermediate- and poor-risk previously treated advanced RCC; and unresectable malignant pleural mesothelioma.10,11

Development of other anti-PD-1 and anti-PD-L1 antibodies and exploration of activity in multiple malignancies followed the initial reports of nivolumab activity in advanced disease. Activity in NSCLC provided proof of concept that these agents could be effective outside melanoma and RCC. In metastatic NSCLC, the estimated 5-year overall survival (OS) rate for patients treated with first-line pembrolizumab monotherapy was nearly twice as high among patients with PD-L1-high (tumor proportion score ≥ 50%) disease as it was for those...
who received platinum-based chemotherapy, according to updated results from the phase 3 KEYNOTE-024 trial (NCT02142738) presented at the European Society for Medical Oncology Virtual Congress 2020. The OS rate was 31.9% for participants who received pembrolizumab (n = 154) versus 16.3% among those who had chemotherapy (n = 151). The median OS was 26.3 months (95% CI, 18.3-40.4) in the pembrolizumab arm compared with 13.4 months (95% CI, 9.4-18.3) in the chemotherapy group.\textsuperscript{12}

Julie R. Brahmer, MD, who presented the findings at the conference and was among the first investigators to study anti–PD-1 in clinic, is among the speakers at the upcoming PER\textsuperscript{8} meeting. She is codirector of the Upper Aerodigestive Department at the Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins Medicine in Baltimore, Maryland.

“I think since the original approval for second-line treatment for metastatic NSCLC [in 2015], we’ve seen an explosion of indications that are making a difference in long-term survival with metastatic disease and now for patients with advanced but unresectable disease after chemotherapy and radiation,” Brahmer said in an interview with OncologyLive\textsuperscript{8}. “We’ve got a long way to go…we just haven’t been out long enough with these checkpoint inhibitors. I think they have changed the face of treating lung cancer.”

Brahmer theorizes that ICIs have made the significant inroads in NSCLC because patients with a history of smoking have a high tumor mutational burden. “When you take the brakes off [with] these checkpoint inhibitors, it allows the immune system to target that kind of cancer,” she said.

**ICI MILESTONES MULTIPLY**

The agenda for the December conference reflects broad use of these drugs. The sessions will look at practical applications in clinic for lung cancer, head and neck cancers, genitourinary malignancies, gastrointestinal malignancies, hematologic malignancies, and breast and ovarian cancers.

“Checkpoint inhibitors are used in most solid tumor malignancies with a few exceptions,” Sznol said. “But even in very resistant tumors, such as pancreatic cancer, that could change soon. For example, promising phase 2 data were presented for the combination of chemotherapy, anti-CD40, and nivolumab. Microsatellite-stable colon cancer remains a challenge, but I’m optimistic that continued preclinical and clinical research will eventually lead to an effective immunotherapy option.”

In June 2020, the FDA approved pembrolizumab as a first-line treatment for patients with unresectable or metastatic MSI-H or dMMR colorectal cancer. The announcement marked the first immunotherapy approval for this patient population as a first-line treatment without administering chemotherapy.\textsuperscript{13}

A key development to be discussed at the conference is the FDA’s June 2020 accelerated approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid malignancies with a high tumor mutational burden \((\geq 10\) mutations per megabase\) whose disease has progressed after prior therapy and who do not have alternative treatment options.\textsuperscript{14} In 2017, pembrolizumab’s approval for use in advanced solid tumors in patients with the MSI-H/dMMR biomarker marked the first example of a tissue site–agnostic FDA approval of a treatment based on a patient’s tumor biomarker status rather than on histology.\textsuperscript{15}

Many new combinations are coming to the fore with anti–PD1/PD-L1 drugs and VEGFR inhibitors, Sznol noted. In RCC, axitinib (Inlyta), which inhibits VEGFR1/2/3, is approved as first-line treatment for patients with advanced disease in combination with pembrolizumab and with avelumab (Bavencio), a PD-L1 inhibitor, respectively.\textsuperscript{16}

Updated results from the phase 3 KEYNOTE-426 trial (NCT02853331), presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, demonstrated that median OS was not reached in patients who received the combination of pembrolizumab plus axitinib versus 35.7 months among those treated with sunitinib (Sutent), leading to a 32% reduction in the risk of death (HR, 0.68; 95% CI, 0.55-0.85; \(P < .001\)). The 2-year OS rate was 74% and 66% in those who received the combination compared with sunitinib, respectively.\textsuperscript{17}

In the phase 3 JAVELIN Renal 101 trial (NCT02684006), OS findings were still immature but favored the combination of avelumab plus axitinib across prespecified subgroups of patients with previously untreated advanced RCC, according to updated findings reported in *Annals of Oncology*. In the overall population, the median progression-free survival was 13.3 months (95% CI, 11.1-15.3) with the combination versus 8.0 months (95% CI, 6.7-9.8) with sunitinib, which translated into a 31% reduction in the risk of progression or death (HR, 0.69; 95% CI, 0.574-0.825; 1-sided \(P < .0001\)).\textsuperscript{18}

In HCC, the combination of atezolizumab (Tecentriq), an anti–PD-L1 agent, plus bevacizumab (Avastin), a VEGF inhibitor, gained FDA approval in May 2020 for patients who had not previously received systemic therapy, based on findings from the phase 3 IMbrave150 trial (NCT03434379).\textsuperscript{19} The combination reduced the risk of death by 42% compared with sorafenib (HR, 0.58; 95% CI, 0.42-0.79; \(P = .0006\)). OS at 12 months was 67.2% (95% CI, 61.3%-73.1%) with atezolizumab plus bevacizumab and 54.6% (95% CI, 45.2%-64.0) with sorafenib. Median OS was not estimable (NE) with the combination versus 13.2 months (10.4-NE) with sorafenib.\textsuperscript{20}

Most recently, on July 30, 2020, the FDA approved atezolizumab in combination with 2 targeted therapies, cobimetinib (Cotellic) and vemurafenib (Zelboraf), for patients with BRAF V600-mutant unresectable or metastatic melanoma.\textsuperscript{21}

**NEW DRUGS AND BIOMARKERS TOP RESEARCH AGENDA**

In terms of research priorities, a need exists for greater insight into which patients are most likely to respond to these therapies, Sznol said. “I think what we’re lacking now is just the predictive biomarkers. It’s really possible that all these combinations are working, but they’re working in small numbers of patients. Without having the biomarkers to identify those patients, the phase 2 combination trials in PD-1/PD-L1 resistant/refractory patients will likely yield low response rates. If we run trials with unselected patients in phase 3, those signals may be too small to detect.”
Immunotherapy

Although some combination regimens have clearly proved their worth, investigators also do not yet know which drug in a given regimen is most effective or even whether one is effective at all. For example, there is no way to know, as with the nivolumab-ipilimumab combination in previously untreated patients, whether the anti–PD-1 therapy or the anti–CTLA-4 agent—or both—is shrinking the tumor or in what proportion, Sznol said.

To Wolchok, a 2014 Giants of Cancer Care® award winner, Sznol is the perfect individual to help lead the way in improving the efficacy of immunotherapeutic regimens. “We’ve got our work yet cut out for us,” said Wolchok, who is the Lloyd I. Old/Virginia and Daniel K. Ludwig Chair in Clinical Investigation and chief of the Immuno-Oncology Service at MSK in New York, New York. “The next questions we have to answer are: What do [ICIs] need to be combined with? What are the immunologic needs for those not responding to the current therapy?

“I think Mario’s dedication to clinical investigation, to new medicine and new pathways, is critical. Serving as president for SITC—that’s a role he’s really perfect for. He’s a senior statesperson in a field he helped to create,” noted Wolchok, who also is director of the Parker Institute for Cancer Immunotherapy at MSK. “I think having Mario as a leader of that organization really feeds into many of his strengths. He’s a thoughtful clinician, he has great scientific knowledge of the area, he’s very personable, and he’s also a wonderfully supportive voice for colleagues, especially younger colleagues.”

Although Sznol spends 40% to 50% of his time seeing patients in clinic, he and his colleagues at Yale are busy at work on novel therapies. “We’re becoming more and more interested in strategies to modulate antigen-presenting cells and myeloid cells within the tumor microenvironment. So my colleagues have looked at, for example, APX005M, a monoclonal agonist antibody that binds to CD40 together with nivolumab, and more recently APX005M combined with nivolumab and a CSF1 receptor antagonist. Whether that’s going to be the right answer or not, we don’t know,” Sznol said. “We’re about to start a trial of anti–CD40 [therapy] together with anti–PD-1 [and anti–CTLA-4 in the frontline setting],” he added. “And we’re very excited about that.”

The phase 1 study (NCT04495257) will evaluate APX005M plus nivolumab and ipilimumab in treatment-naïve patients with advanced melanoma or RCC.

Investigators are also looking at how cytokines can combine with ICIs, Sznol said. He and his colleagues were involved with early development of bempegaldesleukin (Bempeg; NKTR-214), a pegylated form of IL-2.22 The phase 3 PIVOT IO 001 trial (NCT03635983) is evaluating bempegaldesleukin in combination with nivolumab versus nivolumab monotherapy and seeks to enroll 764 patients with previously untreated unresectable or metastatic melanoma. “There are many different exciting opportunities for combinations,” Sznol said. “But we can participate in only a small fraction of the big world of things that can be done. I don’t know that we have any better information or intuition about what will end up working in resistant/refractory patients, but we are fortunate to be part of an outstanding community of investigators around the world. Hopefully, together we will find effective new immune therapies for patients.”

For a full list of references, see the article at Onclive.com.
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Myelofibrosis Paradigm Slated to Expand With Investigative Therapies

by KRISTI ROSA

THE MYELOFIBROSIS PIPELINE IS bursting with novel agents and combinations that have been developed with the goal of helping patients live longer rather than controlling their disease, said Srdan Verstovsek, MD, PhD, who added that phase 3 trials are underway to bring more options into the clinic.

The National Comprehensive Cancer Network guidelines for the treatment of patients with myelofibrosis are based on risk of death, as well as symptoms and signs, said Verstovsek. Patients who are determined as higher risk should be referred for transplant. For those who are not candidates for transplant, ruxolitinib (Jakafi), fedratinib (Inrebic), or a clinical trial is recommended. Patients who are lower risk and asymptomatic should undergo observation or consider a clinical trial, whereas those who are lower risk and symptomatic should consider a clinical trial, ruxolitinib, ropemginterferon α-2a, or hydroxyurea.

“These drugs do not fulfill all the needs [that exist in this disease]—far from that; that’s why we have clinical trials listed almost everywhere,” said Verstovsek, director of the Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms and chief, section for myeloproliferative neoplasms, in the department of leukemia at The University of Texas MD Anderson Cancer Center in Houston (TABLE). “A huge number of new medications are being tested that target different parts of the disease biology; it’s not just about the inhibition of the JAK/STAT pathway alone [anymore]. Many other drugs are in development and most of them are being tested in the second-line setting, after JAK inhibitors.”

JAK INHIBITORS UNDER INVESTIGATION

To date, 2 JAK inhibitors have received approval for use in patients with myelofibrosis: ruxolitinib and fedratinib. Now fedratinib is under exploration in the second-line setting and several other agents also have emerged.

In a virtual presentation during the Society of Hematologic Oncology 2020 Virtual Annual Meeting, Verstovsek highlighted ongoing phase 3 efforts and agents that are generating excitement.1

JAK inhibitors under investigation

1. In the phase 3 PACIFICA trial (NCT03165734), investigators are examining pacritinib compared with physician’s choice in patients with myelofibrosis and severe thrombocytopenia with a platelet count of less than 50,000 mL.2 “This JAK inhibitor is not myelosuppressive; it can improve the signs and symptoms of the disease, even in patients with platelets below 50,000 mL,” Verstovsek said.

Additionally, momelotinib is under examination in the second-line setting in the phase 3 MOMENTUM trial (NCT04173494). In this study, 180 patients who received previous treatment with a JAK inhibitor and who have a total symptom score of 10 or greater and are anemic are undergoing a 2:1 randomization between momelotinib at 200 mg daily versus danazol at 600 mg daily followed by momelotinib at 200 mg daily.3

“Momelotinib appears to improve anemia,” said Verstovsek. “Therefore, this is a study for patients who do not feel well and have anemia; this is a different way of thinking when it comes to JAK inhibitors.”

Luspatercept

Luspatercept-aamt (Reblozyl), which received FDA approval in April 2020 for myelodysplastic syndromes-associated
anemia, is now under exploration in patients with myelofibrosis-associated anemia in a phase 2 trial.4 “This is a huge area of unmet need; we don’t have any drug approved for anemia, and here we have a study underway,” said Verstovsek.

A total of 74 patients were enrolled; 41 did not receive concomitant ruxolitinib at study entry. Results indicated that the cohorts who received a stable dose of ruxolitinib (cohorts 3A and 3B) experienced better responses.

These data led to the planned launch of the double-blind, randomized, phase 3 INDEPENDENCE trial examining the safety of luspatercept compared with placebo in patients with myeloproliferative neoplasm-associated myelofibrosis who are on concomitant JAK2 inhibitor therapy and require red blood cell transfusions.

**CPI-0610**

Another agent that has emerged in recent years is the BET inhibitor CPI-0610; this potent and selective small molecule that developed to encourage antitumor activity by inhibiting a function of BET proteins to reduce the expression of abnormally expressed genes in cancer.5

In the phase 2 MANIFEST trial (NCT02158858), investigators are examining CPI-0610 in combination with ruxolitinib in patients with myelofibrosis who had not received prior treatment with JAK inhibitors (arm 3). These patients had a Dynamic International Prognostic Scoring System (DIPSS) score of intermediate-2 or higher and a platelet count of 100 x 10^9/L or greater. In arms 1 and 2 of the trial, CPI-0610 is being examined as a mono-therapy and as an add-on to ruxolitinib, respectively, in patients who had received prior JAK inhibitors.

Results showed that at the April 17, 2020, data cutoff, 63% (n = 19/30) of patients experienced a 35% or greater spleen volume reduction (SVR35) with a median percentage change of 53%. Moreover, 59% (n = 17/29) of patients achieved a 50% or greater total symptom score improvement with a median percentage change of 64%).6 These data have led to the launch of a global phase 3 trial, which will examine CPI-0610 plus ruxolitinib versus placebo plus ruxolitinib in patients with primary myelofibrosis or post-essential thrombocytopenia/polycythemia vera who have not received JAK inhibitors, noted Verstovsek.

**NAVITOCLAX**

Another agent, navitoclax, is a novel small molecule that binds with high affinity to BCL-XL, BCL-2, and BCL-W, leading to cell death and apoptosis.7 Because BCL-XL inhibition possesses the potential to thwart fibrosis growth in the bone marrow, and the combination of JAK inhibitors and BCL-XL/BCL-2 has been shown to have a synergistic effect in eliminating JAK-mutated cells, investigators set out to examine navitoclax in combination with ruxolitinib. The hypothesis was that the combination would overcome resistance to JAK2 inhibition, explained Verstovsek.

In a single-arm, multicenter, open-label phase 2 trial, investigators examined the combination in patients with myelofibrosis. Navitoclax was administered at a starting dose of 50 mg once daily and the dose was increased on a weekly basis, in a stepwise fashion, up to a maximum dose of 300 mg once daily based on patient tolerability and platelet count.

Results showed that 26.5% (n = 9/34) of patients achieved an SVR35 at week 24 with the combination. Fifty-three percent (n = 18/34) of patients experienced resolved palpable splenomegaly during study treatment, and 29.4% (n = 10/34) showed a grade 1 or higher reduction in bone marrow fibrosis.8 “These are the best results that I have seen so far with an add-on approach,” said Verstovsek. “In the same setting, we see that quality of life also gets improved. This is a signal that needs to be explored.”

Other phase 3 studies are planned to examine this agent further. In the TRANSFORM-1 trial (NCT04472598), navitoclax plus ruxolitinib will be compared

### TABLE. Select Studies Recruiting Patients in Myelofibrosis

<table>
<thead>
<tr>
<th>ClinicalTrials.gov identifier (phase)</th>
<th>Patient population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03165734 (PACIFICA; phase 3)</td>
<td>DIPSS intermediate-1 to high-risk PMF, PPV-MF, or PET-MF with no or limited exposure to JAK2 inhibition and severe thrombocytopenia (platelet count &lt; 50,000/µL) (N = 348)</td>
<td>Arm 1: Pacritinib monotherapy</td>
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<td>Arm 2: Physician’s choice of 1 of the following: corticosteroids, hydroxyurea, danazol, or low-dose ruxolitinib</td>
</tr>
<tr>
<td>NCT04173494 (MOMENTUM; phase 3)</td>
<td>Patients with primary MF, PPV-MF, or PET-MF who are symptomatic and anemic and have received prior JAK inhibition (N = 180)</td>
<td>Arm 1: Momelotinib plus danazol-matched placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: Danazol plus momelotinib-matched placebo</td>
</tr>
<tr>
<td>NCT03194542 (phase 2)</td>
<td>Patients with myeloproliferative neoplasm-associated MF and anemia with or without RBC transfusion dependence (N = 103)</td>
<td>Arm: Luspatercept monotherapy</td>
</tr>
<tr>
<td>NCT02158858 (MANIFEST; phase 2)</td>
<td>Patients with DIPSS intermediate-2 or higher MF who have or have not received prior treatment with a JAK2 inhibitor (N = 271)</td>
<td>Arm 1: CPI-0610 monotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: CPI-0610 added onto ruxolitinib</td>
</tr>
<tr>
<td></td>
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<td>Arm 3: CPI-0610 and ruxolitinib</td>
</tr>
<tr>
<td>NCT04472598 (TRANSFORM-1; phase 3)</td>
<td>DIPSS-intermediate-2 or high-risk JAK2 and BET inhibitor-naïve primary or secondary MF, PPV-MF, or PET-MF (N = 230)</td>
<td>Arm 1: Navitoclax plus ruxolitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2: Ruxolitinib</td>
</tr>
</tbody>
</table>

DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PET, post-essential thrombocytemia; PMF, primary myelofibrosis; PPV, post-polycythemia; RBC, red blood cell.
with ruxolitinib plus placebo in patients with myelofibrosis who have not received previous JAK2 inhibitors. In TRANSFORM-2 (NCT04468984), investigators will compare navitoclax/ruxolitinib versus best available therapy in patients with myelofibrosis who have been treated with and relapsed on or were refractory to JAK2 inhibitor therapy.

**IMETELSTAT**
The first-in-class telomerase inhibitor imetelstat was evaluated at 2 doses, 9.4 mg/kg and 4.7 mg/kg given intravenously every 3 weeks, in patients with DIPSS score of intermediate-2 or high-risk myelofibrosis that was relapsed or refractory to previous JAK inhibition in a phase 2 trial.9

At 24 weeks, 10% (n = 6) of patients who received 9.4 mg/kg of the agent experienced SVR35, whereas 37% (n = 23) of patients who received that dose experienced an SVR of at least 10%. Additionally, at a median follow-up of 27.4 months, the median overall survival was 19.9 months (95% CI, 17.1-not evaluable) in those who received the 4.7 mg/kg dose versus 29.9 months (95% CI, 22.8-not evaluable) in those who received the higher dose.

“The intent is to determine if daratumumab can benefit patients who are African American or not.”

The subgroup analysis sought to elucidate differences in outcomes for Black patients versus White patients based on a primary analysis of the GRIFFIN study (NCT02874742), said Nooka, an associate professor at the Department of Hematology and Medical Oncology at Emory University School of Medicine and medical director at the Winship Cancer Institute of Emory University.2 Historically, Black patients have had poorer outcomes than White patients, although when given equal access to care, they have similar or better outcomes relative to White patients.3,4

The primary end point of the GRIFFIN trial was sCR following allogeneic stem cell transplant and was evaluable in 106 patients of the overall population. The prespecified median follow-up was 13.5 months. The sCR rates favored D-RVd (n = 99) versus RVd (n = 97) at 42.4% versus 32.0%, respectively (OR, 1.57; 95% CI, 0.87-2.82; 1-sided P = .068, meeting the prespecified 1-sided α of 0.10.2

**DATA FROM A SUBGROUP** analysis of the phase 2 GRIFFIN study demonstrated that adding daratumumab (Darzalex) to lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVd) improved depth of response, stringent complete response (sCR), and minimal residual disease (MRD) negativity, in Black patients with newly diagnosed multiple myeloma.

Thirty-two Black patients received either RVd plus daratumumab (D-RVd; n = 18) or RVd (n = 14). Investigators reported that the sCR rate was higher for Black patients who received D-RVd versus RVd (71% vs 33%) at the end of the consolidation phase. The odds ratio was 5.00 (95% CI, 1.10-22.82; 2-sided P = .0353). Similar efficacy was reported in White patients, with higher sCR rates observed with the 4-drug regimen (n = 85) versus the 3-drug regimen (n = 76; 43% vs 34%, respectively). The OR for sCR at the end of consolidation among White patients was 1.46 (95% CI, 0.76-2.82; P = .2620).1

“This analysis is not meant to provide a direct comparison between the Black or the White patients,” said lead author Ajay K. Nooka, MD, MPH, during a presentation at the Society of Hematologic Oncology 2020 Virtual Annual Meeting.1 “The intent is to determine if daratumumab can benefit patients who are African American or not.”

The subgroup analysis sought to elucidate a greater understanding of the differences in outcomes for Black patients versus White patients based on a primary analysis of the
Further, responses continued to deepen at last follow-up. At median follow-up of 22.1 months, sCR rates were 62.6% for patients treated with D-RVd versus 45.4% for those who received RVd, demonstrating that the addition of the anti-CD38 antibody essentially doubled the likelihood of achieving sCR (OR, 1.98; 95% CI, 1.12-3.49; \( P = .0177 \)). Improved MRD-negativity rates were also observed in the intention-to-treat population in 51.0% (51/104) and 20.4% (21/103), respectively; \( P < .0001 \).

“By the end of the consolidation phase, the sCR rate was improved for D-RVd versus RVd in both patient populations,” Nooka said.

RESPONSE DATA SHOW SIMILAR IMPROVEMENT

The overall response rate (ORR) was 100% and 94% for D-RVd and RVd, respectively, in Black patients, with similar findings reported for White patients (TABLE). “The responses deepened over time in both the Black patients and White patients with a complete response of 21% by the end of transplant, which increased to 86% by the end of consolidation, with 71% of these found to be stringent complete responses,” Nooka said. This improvement was observed for all time points among Black patients who received daratumumab.

By the end of posttransplant consolidation, MRD negativity at the 10-5 threshold was significantly higher in the daratumab arm, at 36% with D-RVd compared with 16% in the RVd group. In Black patients, MRD negativity was 49% in the D-RVd group compared with 16% in the RVd group.

Regarding toxicities, the most common any-grade treatment emergent adverse events (TEAEs) in Black patients were neutropenia (57%), anemia (50%), leukopenia (43%), thrombocytopenia (43%), and lymphopenia (36%) for the D-RVd arm. In White patients, toxicity rates were similar with 58% experiencing neutropenia, followed by thrombocytopenia (45%), leukopenia (25%), anemia (34%), and lymphopenia (30%) for the D-RVd arm. The rate of grade 3 or 4 TEAEs in the D-RVd versus RVd arms was 79% versus 83% for Black patients, and 83% versus 76% for White patients, respectively.

“Overall, higher rates of grade 3 and 4 neutropenia, leukopenia, and thrombocytopenia were observed in Black patients treated with D-RVd than in White patients,” Nooka said.

Treatment discontinuation occurred in 36% and 28% of Black patients in the D-RVd and RVd arms, respectively, and in 11% and 16%, respectively, of White patients. Among Black patients, 5 patients in each treatment arm discontinued RVd, with the most frequent cause attributed to peripheral neuropathy or neuralgia. Infusion-related reactions to daratumumab occurred in 29% of Black patients and 45% of White patients and were generally mild (grade 1 or 2). There were zero deaths reported for either subgroup. Overall, the safety profile of D-RVd among Black patients was consistent with that of White patients, Nooka said.

“In Black patients with newly diagnosed multiple myeloma, using D-RVd as induction and consolidation therapy improved depth of response, including the rate of sCR and MRD negativity,” Nooka said. “These results support D-RVd as a potential new standard of care for Black patients who are transplant eligible and newly diagnosed.”

REFERENCES


MORE ON OncLive.com

SYMPATICO Evaluates Frontline Ibrutinib and Venetoclax Combo in MCL

The open-label arm of the 3-part phase 3 SYMPATICO trial is evaluating the combination of ibrutinib (Imbruvica) and venetoclax (Venclexta) in previously untreated patients with mantle cell lymphoma (MCL). Lead author, Michael L. Wang, MD, discusses the rationale for the trial and the preclinical data that demonstrated synergistic antitumor activity through dual inhibition of the BTK and BCL-2 pathways with the combination of ibrutinib and venetoclax.

For more coverage of the Society of Hematologic Oncology Virtual Annual Meeting, visit: https://www.onclive.com/conference/soho
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**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, pruritus, 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 ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%).

- In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%).

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.

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 effective 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 bound 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 hematologic 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.

cp-143279v1


2. DARZALEX™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

**INDICATIONS AND USAGE**

DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:

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- 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.

**CONTRAINDICATIONS**

DARZALEX FASPRO™ is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

**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 (see Dosage and Administration (2.3) in Full Prescribing Information). 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 (see Dosage and Administration (2.3) in Full Prescribing Information).

**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.

**Neutropenia**

Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions). 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 4 neutropenia were observed.

**Thrombocytopenia**

Daratumumab may increase thrombocytopenia induced by background therapy (see Adverse Reactions). 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 who are reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

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 bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References]. The determination of a patient’s ABO and Rh blood type are impacted [see Drug Interactions].

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 (see Dosage and Administration (2.1) in Full Prescribing Information).

**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 [see Drug Interactions]. 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 following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

**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.
Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with bortezomib, melphan and prednisone (D-VMP) in PLEIADIES.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphan and Prednisone*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-VMP (N=87).

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADIES (see Clinical Studies (14.1) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/50,000 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). 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, dyspnea, and blood creatinine increased. 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 PLEIADIES.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
</tr>
<tr>
<td>Track pain</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-Rd (N=65).

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/50,000 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). 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 1 patient were general physical health deterioration, septic shock, and respiratory failure.

Permanently 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.

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

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

Table 4 summarizes the adverse reactions in patients who received DARZALEX FASPRO or intravenous Daratumumab in COLUMBA.

Table 4: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24</td>
<td>1%</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>8</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>1%</td>
</tr>
<tr>
<td>Infusion reactionsb</td>
<td>13</td>
<td>2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0%</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughf</td>
<td>8</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>1%</td>
</tr>
</tbody>
</table>

a Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.

b Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.

c Fatigue includes asthenia, and fatigue.

d Infusion reactions includes terms determined by investigators to be related to infusion.

e Cough includes cough, and productive cough.

f Dyspnea includes dyspnea, and dyspnea exertional.

g Only grade 3 adverse reactions occurred.

h Grade 5 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO included:

- General disorders and administration site conditions: injection site reaction, peripheral edema
- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, muscle spasms
- Gastrointestinal disorders: constipation, vomiting, abdominal pain
- Metabolism and nutrition disorders: decreased appetite, hypoglycemia, hypocalcemia, dehydration
- Psychiatric disorders: insomnia
- Vascular disorders: hypertension
- Nervous system disorders: dizziness, peripheral sensory neuropathy, paresthesia
- Infections: bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B reactivation
- Skin and subcutaneous tissue disorders: pruritus, rash
- Cardiac disorders: atrial fibrillation
- Respiratory, thoracic and mediastinal disorders: pulmonary edema

Table 5: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab 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></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>1%</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>13</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>0%</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>1%</td>
</tr>
</tbody>
</table>
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

Table 6 summarizes the laboratory abnormalities in COLUMBA.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO+</th>
<th>Intravenous Daratumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>65%</td>
<td>19%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>59%</td>
<td>36%</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>55%</td>
<td>19%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>43%</td>
<td>16%</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>42%</td>
<td>14%</td>
</tr>
</tbody>
</table>

+ Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=256).

Immuneogenicity
As with all therapeutic proteins, there is the potential for immunoogenicity. 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 as monotherapy 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 had limitations in detecting anti-daratumumab antibodies in the absence of the presence of combinations of other antibodies.

Treatment-emergent anti-HuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (18/1952) of patients who received DARZALEX FASPRO as part of a combination therapy. The anti-HuPH20 antibodies did not appear to affect daratumumab exposures. None of the patients who tested positive for anti-HuPH20 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

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 dithiothreitol (DTT) to disrupt the high-affinity 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/Rh-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 assays may occur for patients with high kappa myeloma protein impairment. The analysis 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 2% to 3% per pregnancy.

Embryo-Fetal Toxicity
DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations]. 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 embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously 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 from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

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 doses.

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. Infection control during live vaccines to neonates and infants exposed to daratumumab in utero until a hematologic 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 5 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), fetal-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 embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously during organogenesis, which is 45 times higher than the human dose.

Hepatitis B Virus (HBV) Reactivation
Advises patients to inform their healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again. [See Adverse Reactions].

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Horsham, PA 19044
U.S. License Number 1894
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Investigators Tackle New NSCLC Target With Glutaminase Inhibitor

by DENISE MYSHKO

TELAGLENASTAT (CB-839), a novel drug that targets a key metabolic pathway, has shown encouraging antitumor activity in several cancer types. Now, investigators have launched the phase 2 KEAPSAKE trial to evaluate the agent in combination with standard-of-care chemoimmunotherapy as a first-line treatment for patients with metastatic nonsquamous non–small cell lung cancer (NSCLC) with KEAP1 or NRF2 mutations.

Patients whose tumors harbor these mutations do not respond well to treatment, even with the best standard of care, said Naiyer A. Rizvi, MD, the principal investigator on the KEAPSAKE study. Rizvi is the Price Family Professor of Medicine, director of thoracic oncology, and codirector of cancer immunotherapy at Columbia University Herbert Irving Comprehensive Cancer Center in New York, New York.

In NSCLC, KEAP1 or NRF2 mutations occur in more than 20% of patients but no drugs that specifically target these alterations have been approved, according to a presentation by Rizvi at the 2020 American Society of Clinical Oncology Virtual Scientific Program. “KEAPI mutations are the third most common tumor mutation in lung adenocarcinoma [after TP53 and KRAS5], so they are very common,” he said. “NRF2 mutations are seen in both squamous and nonsquamous histology.”

Dysregulated activity of the KEAPI/NRF2 pathway promotes tumor growth and survival, investigators have found. “These KEAPI mutations are highly dependent on glutamine metabolism. Glutamine is metabolized to glutamate for DNA protein synthesis but it also converts to glutathione, which protects the cancer cells from oxidative stress,” said Rizvi, who is the research director of the Price Family Comprehensive Center for Chest Care at NewYork-Presbyterian Hospital. “Preclinical models show that if you block glutamine metabolism with telaglenastat, you can increase the oxidative stress within the tumors and allow for potentially better tumor destruction when you give this with standard-of-care treatments.”

In the KEAPSAKE trial (NCT04265534), participants will be randomized to receive telaglenastat in combination with pembrolizumab (Keytruda), a PD-1 inhibitor, plus carboplatin and pemetrexed (Alimta) versus placebo with pembrolizumab and the chemotherapy combination (FIGURE). Telaglenastat will be administered orally with food at 800 mg twice daily in combination with standard-of-care pembrolizumab plus chemotherapy by intravenous (IV) infusion every 3 weeks. Patients will be assessed every 3 months for up to 3 years.

The primary end points are progression-free survival (PFS) per RECIST 1.1 criteria and safety and tolerability of telaglenastat. Secondary end points include objective response rate, duration of response, and overall survival.

The trial results will be stratified by STK11/LKB1 mutational status; alterations in these genes have been associated with lack of response to standard therapy with pembrolizumab. Additionally, KEAPI is significantly co-mutated with STK11. KEAPSAKE, which recently opened for recruitment, is expected to enroll 120 patients in 57 study locations in the United States. Eligible patients must have stage IV nonsquamous NSCLC that has not been previously treated in the metastatic setting and no EGFR, ALK, ROSI, or other actionable mutation for which there is already an approved therapy.

KEAPI/NRF2 mutation status will be determined by next-generation sequencing using the Guardant360 CDx assay, which analyzes genetic alterations in circulating cell-free DNA extracted from the plasma of peripheral whole blood. In August 2020, the FDA approved Guardant360 CDx as a companion diagnostic for osimertinib (Tagrisso) to identify EGFR exon 19 deletions, L858R substitutions, and the T790M.
resistance mutation in patients with NSCLC. The test also is approved as a tumor profiling assay for NSCLC.6

“The testing is an advantage for the patients, even if they don’t have a KEAP1 mutation. They get this commercial assay that looks for not just KEAP1 mutations but other mutations within the panel as well. There is information to be gained no matter what your mutational status is or whether you go on the trial or not,” Rizvi said in an interview.

**EARLY EFFICACY FINDINGS FOR TELAGLENASTAT**

Preclinical testing has shown that loss of KEAP1 activates NRF2 and promotes lung adenocarcinoma. In one study, it was shown that KEAP1/NRF2-mutated cancers are likely to respond to glutaminase inhibition.7

In an ongoing phase 1/2 study (CX-839-004; NCT02777626), telaglenastat was evaluated in combination with the PD-1 inhibitor nivolumab (Opdivo) in patients with advanced NSCLC who progressed on prior PD-1/PD-L1 inhibitor therapy. Patients with KEAP1 mutations had a higher clinical benefit rate (CBR) and longer median PFS than those without these mutations.1

Among participants tested for KEAP1 mutations, the CBR was 75% in those with the alteration (3 of 4 patients) versus 15% in those without it (2 of 13 patients), with CBR defined as a combination of complete and partial responses and stable disease. The median PFS was 6.4 months for patients with the KEAP1 mutation compared with 3.7 months for those with wild-type KEAP1, with responses evaluated using modified RECIST 1.1 criteria for immune-based therapies.1

Additionally, telaglenastat has demonstrated antitumor activity in patients with previously treated advanced or metastatic clear cell renal cell carcinoma (RCC) in the phase 2 ENTRATA trial (NCT03428217). Patients in the double-blind study were randomized 2:1 to telaglenastat in combination with everolimus (Afinitor), an mTOR inhibitor (n = 46), or placebo plus everolimus (n = 23).8

The telaglenastat combination doubled the median PFS to 3.8 months versus 1.9 months with the everolimus combination (HR, 0.64; 95% CI, 0.34-1.20; 1-sided \( P = .079 \)). The most frequently reported grade 3 or higher adverse effects in the treatment arm versus the control group, respectively, were anemia (17.4% vs 17.4%), pneumonia (6.5% vs 4.3%), abdominal pain (6.5% vs 0%), thrombocytopenia (6.5% vs 0%), and fatigue (4.3% vs 8.7%).8

Telaglenastat is currently being evaluated in the phase 2 CANTATA trial (NCT03428217), in which telaglenastat in combination with cabozantinib (Cabometyx) is being compared with placebo plus cabozantinib in patients with previously treated advanced or metastatic RCC. The primary end point is PFS.

Findings from the study, which has completed enrollment of 444 patients, are expected late in 2020 or early in the first quarter of 2021, according to Calithera Biosciences, the company developing telaglenastat.9

“Telaglenastat is also being studied in combination with azacitidine (Vidaza) in a single-arm phase 1/2 study (NCT0347993) in patients with intermediate- and high-risk myelodysplastic syndromes. Findings from an interim analysis involving 19 patients were presented at the 2019 American Society of Hematology Annual Meeting. The regimen demonstrated an overall response rate of 65%, including complete responses of 11%, a 1-year overall survival rate of 50%, and 1-year event-free survival rate of 33%.10

REFERENCES

Early Data Show Neoadjuvant Nivolumab Enhances Electroporation in HCC

by JASON HARRIS

NEOADJUVANT NIVOLUMAB (OPDIVO) shrunk tumors in 29% of patients with hepatocellular carcinoma (HCC) at high risk for recurrence, which may kickstart the ablation effect of electroporation (EP), according to preliminary findings from the phase 2 NIVOLEP trial presented at the 2020 International Liver Cancer Association Virtual Meeting.¹

Percutaneous ablation remains the only nonsurgical curative treatment for patients with HCC. During the past 20 years, advancements in the procedure have allowed physicians to offer the technique to more patients. However, many patients remain ineligible for thermal ablation due to hazardous tumor location or severe comorbidities.

The most recent development, irreversible EP, is a predominantly nonthermal ablative technology that induces apoptosis using high-voltage, low-energy DC current pulses, said Pierre Nahon, MD, PhD, during his presentation.²,³

Investigators of the NIVOLEP trial (NCT03630640) set out to optimize the efficacy of EP in patients with HCC using nivolumab as neoadjuvant therapy. The first 20 patients enrolled to the study were included in the preliminary neoadjuvant phase response data. Patients received 2 infusions of nivolumab and underwent radiological or pathological evaluations, or both, at baseline, following neoadjuvant treatment. Investigators identified a total of 37 HCC nodules; the mean size of largest nodule was 31.4 mm.¹

Radiological reduction was observed in 11 (29%) nodules and 25 (68%) nodules were stable, defined as no change in size, following neoadjuvant treatment. Further, the results showed that all patients received neoadjuvant nivolumab without experiencing serious adverse events (AEs) and 19 patients went on to receive successful curative EP without delay.¹

“The preliminary analysis of [data] from the neoadjuvant phase shows that there is active recruitment of CD8+ lymphocytes within the tumor and macroenvironment which may potentialize the ablation effect,” said Nahon, an associate professor in hepatology at University Paris 13, in France. “We also observed potential antitumor activity with reduction in size and/or HCC necrosis before ablation.”

In a case analysis of 1 patient, Nahon explained that pathologic analysis following treatment with nivolumab showed near-complete necrosis of the tumor with major infiltration by polymorphonuclear, lymphocyte, and foam cells associated with extensive fibrosis. “These histological features suggest almost complete tumor regression,” Nahon added.

Seventeen nodules were assessed for both radiological and pathological modification. Of those, 3 (17%) demonstrated a tumor response pattern and 4 (23%) had an isolated increase in peritumoral and intratumoral infiltrating lymphocytes. In total, 9 patients (53%) had either radiological or pathological modification following nivolumab infusion. One patient experienced progression.

“Induced radiological and pathological changes were reported in a substantial number of patients—nearly half of this small sample size. This suggests that neoadjuvant nivolumab may have antitumoral or immunomodulation effect in these patients, which will be correlated with their outcomes,” said Nahon.

Investigators initiated NIVOLEP to evaluate the combination of neoadjuvant or adjuvant biotherapy with EP in patients with Barcelona clinic liver cancer stage A HCC. The primary end point is recurrence-free survival (RFS) at 2 years. Target enrollment is 50 patients across 6 medical centers in France. Patients will receive 2 doses of neoadjuvant nivolumab followed by EP, then 12 monthly doses of adjuvant nivolumab for 1 year. Follow-up will occur every 3 months during the subsequent year.

NAVIGATING PRIOR EFFICACY DATA

EP is particularly valuable for patients whose liver tumors are not accessible for surgery or who are contraindicated for surgery, and for patients with very early HCC or very small tumors.⁴

In 2017, Sutter et al, published results from a retrospective study of the safety and efficacy of EP in patients with HCC who were not candidates for surgery and were ineligible for thermal ablative techniques. In total, 75 tumors were completely ablated. Specifically, 58, 67, and 69 were completely ablated tumors were ablated following 1, 2, and 3 EP procedures, respectively. At a median follow-up of 9 months, the 6- and 12-month overall local tumor progression-free survival rates were 87% (95% CI, 77%-93%) and 70% (95% CI, 56%-81%), respectively.³

“What was observed was that 48 hours after the ablation, something happens in the nontumoral liver, it corresponds to systemic effects and immunogenicity change, which are far more increased in electroporation compared with radiofrequency ablation with an influx of inflammatory,” Nahon said of the study results from Sutter et al. The hypothesis to combine immunotherapy with EP for these difficult-to-treat patients grew from this observation, Nahon said of the NIVOLEP study design.

The technique also holds potential for patients who present with comorbidities. Unlike thermal procedures, the collagenic skeleton and the microvessels of surrounding nontumorous tissue are spared using EP.⁵

Findings from a 2016 study of 55 patients with Child-Pugh B HCC showed that, compared with microwave ablation, those who received EP had shorter hospital stays and a lower 90-day readmission rate. Furthermore, EP was better tolerated and the 6-month success rates were nearly identical at 97% and 100%, respectively, making it a more suitable option for fragile patients.⁶

For a full list of references, see the article at https://bit.ly/2GNhTkS.
LEARN MORE ABOUT TRODELVY™
(sacituzumab govitecan-hziy) TODAY!

Join Dr. Hope S. Rugo, MD, to learn more about TRODELVY. TRODELVY is the first ADC FDA approved for adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease.

INDICATION
TRODELVY™ (sacituzumab govitecan-hziy) is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

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

IMPORTANT SAFETY INFORMATION

WARNING: NEUTROPENIA AND DIARRHEA
Severe neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.

Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.

See additional Important Safety Information continued on the next page.
Pregnancy

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Lactation

There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfeeding child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Adverse Reactions

Most common adverse reactions (incidence ≥25%) in patients with mTNBC are nausea (69%), neutropenia (64%), diarrhea (63%), fatigue (57%), anemia (52%), vomiting (49%), alopecia (38%), constipation (34%), rash (31%), decreased appetite (30%), abdominal pain (26%), and respiratory infection (26%).

Use in Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele and 11% (16/149) in patients homozygous for the wild-type allele.

Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.

Embryo-Fetal Toxicity

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

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**WARNINGS AND PRECAUTIONS**

**CONTRAINDICATIONS**

- Severe neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay [see Warnings and Precautions].
- Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide [see Warnings and Precautions]. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.

**WARNINGS AND PRECAUTIONS**

**Neutropenia**

TRODELVY can cause severe or life-threatening neutropenia. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Febrile neutropenia occurred in 6% (24/408) patients treated with TRODELVY, including 8% (9/108) patients with mTNBC after at least two prior therapies. Less than 1% (1/908) of patients had febrile neutropenia leading to permanent discontinuation.

The incidence of Grade 1–4 neutropenia was 64% in patients with mTNBC (n=108). In all patients treated with TRODELVY (n=408), the incidence of Grade 1–4 neutropenia was 54%; Grade 4 neutropenia occurred in 13%. Less than 1% (2/408) of patients permanently discontinued treatment due to neutropenia.

**Diabetes**

TRODELVY can cause severe diabetes. Withhold TRODELVY for Grade 3 diabetes at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1.

At the onset of diabetes, evaluate for infectious causes and if dialyzer, promptly initiate loperamide, 4 mg initially followed by 2 mg every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate pretreatment (e.g., atropine) for subsequent treatments.

Diabetes occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3–4 occurred in 9% (9/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment because of diabetes. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY.

**Hypersensitivity**

TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical practice.

**DIARRHEA**

Diarrhea occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3–4 occurred in 9% (9/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Diarrhea occurred in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY.

**VOMITING**

Vomiting occurred in 77% (93/121) of patients with mTNBC and 74% (16/22) of all patients treated with TRODELVY. In each population, events of Grade 3–4 occurred in 9% (9/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Forty-five percent (45%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 13% of patients treated with TRODELVY, with 24% having one dose reduction and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/life-threatening neutropenia.

**Sexual Function**

TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to discontinuation were anaphylaxis, anemia/fatigue, and headache (each <1%, 1 patient each for event). Fifty-four percent (54%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 13% of patients treated with TRODELVY, with 24% having one dose reduction and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/life-threatening neutropenia.

Adverse reactions occurring in ≥10% of patients with mTNBC in the IMMU-132-01 study are summarized in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Adverse Reactions in ≥10% of Patients with mTNBC in IMMU-132-01</th>
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<tbody>
<tr>
<td><strong>Any adverse reaction</strong></td>
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<tr>
<td>Adverse Reaction</td>
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<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Nausea</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Mucositis</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Pruritus</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Decreased appetite</td>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Hypomagnesemia</td>
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<tr>
<td>Hypokalemia</td>
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<tr>
<td>Hypophosphatemia</td>
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<tr>
<td>Dehydration</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<tr>
<td>Alopecia</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Pruritus</td>
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<tr>
<td>Dry Skin</td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Neuropathy</td>
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<tr>
<td>Dysequisia</td>
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<tr>
<td>Infections and infestations</td>
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<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Respiratory infection</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Arthralgia</td>
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<tr>
<td>Pain in extremity</td>
</tr>
</tbody>
</table>
CONTRAINDICATIONS

Embryo-Fetal Toxicity

Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk of congenital anomalies. Decreased function alleles other than UGT1A1*28 may be present in certain populations. Of the patients who received TRODELVY, 19/108 (18%) patients with mTNBC and 144/408 (35%) of all patients were ≥ 65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

Hepatic Impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin less than or equal to 1.5 ULN and AST/ALT < 3 ULN). The exposure of TRODELVY in patients with mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN, or bilirubin greater than 1.0 to 1.5 ULN and AST of any level; n=12) was similar to patients with normal hepatic function (bilirubin or AST less than ULN; n=48). The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin > 1.5 ULN, or AST and ALT > 3 ULN, or AST and ALT > 5 ULN and associated with liver metastases. No dedicated trial was performed to investigate the tolerability of TRODELVY in patients with moderate or severe hepatic impairment. No recommendations can be made for the starting dose in these patients.

OVERDOSE

In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

Pharmacogenomics

SN-38 is metabolized via UGT1A1. Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from TRODELVY (see Warnings and Precautions). Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations.

PATIENT COUNSELING INFORMATION

Adviser the patient to read the FSIR-approved patient labeling (Patient Information).

Neutropenia

Adviser patients of the risk of neutropenia. Instruct patients to immediately contact their healthcare provider if they experience fever, chills, or other signs of infection (see Warnings and Precautions).

Diarrhea

Adviser patients of the risk of diarrhea. Instruct patients to immediately contact their healthcare provider if they experience diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours following the infusion (see Warnings and Precautions).

Hypersensitivity

Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, or tongue swelling; urticaria; difficulty breathing; lightheadedness, dizziness, chills, or rigors; wheezing, pruritus, flushing, rash; hypotension or fever, which occur during or within 24 hours following the infusion (see Warnings and Precautions).

Nausea/Vomiting

Adviser patients of the risk of nausea and vomiting. Premedication according to established guidelines with a two or three drug regimen for prevention of chemotherapy-induced nausea and vomiting (CMO) is also recommended. Additional antiemetics, opioids, and other supportive measures may also be employed as clinically indicated. All patients should receive take-home medications for preventing and treating delayed nausea and vomiting, with clear instructions. Instruct patients to immediately contact their healthcare provider if they experience uncontrolled nausea or vomiting (see Warnings and Precautions).

Embryo-Fetal Teratogenicity

Adviser female patients to contact their healthcare provider if they are pregnant or become pregnant. Infor female patients of the risk to a fetus and potential loss of the pregnancy (see Use in Specific Populations).

Contraception

Adviser female patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of TRODELVY (see Use in Specific Populations).

Adviser male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TRODELVY (see Use in Specific Populations).

Lactation

Adviser women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY (see Use in Specific Populations).

Infertility

Adviser females of reproductive potential that TRODELVY may impair fertility (see Use in Specific Populations).

Manufactured by:
Immunomedics, Inc.
300 The American Road
Morris Plains, NJ 07950, USA U.S. License No. 1737

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01 (cont’d)

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>TRODELVY (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>22</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>21</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>26</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
</tr>
</tbody>
</table>

Seated per NCI CTCAE v. 4.0
*Including abdominal pain, distention, pain (upper), discomfort, tenderness
*Including somnolence, drowsiness, and neuromuscular inflammation
*Including nycturia, nocturia, and peripheral edema
*Including rash, maculopapular, erythematous, generalized rash, dermatitis xerotic, skin discoloration, irritation, and exfoliation
*Including gastrointestinal, hematologic, and lymphoid tissue effects
*Includes cough and production cough
*Includes dyspnea and exertional dyspnea

Table 3: Laboratory Abnormalities observed in > 10% of Patients while receiving TRODELVY

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TRODELVY (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>93</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>91</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>82</td>
</tr>
<tr>
<td>Increased activated partial thromboplastin time</td>
<td>60</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>30</td>
</tr>
</tbody>
</table>

Chemistry

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TRODELVY (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased alkaline phosphatase</td>
<td>57</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>51</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>49</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>48</td>
</tr>
<tr>
<td>Decreased aspartate aminotransferase</td>
<td>45</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>39</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>35</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>30</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>29</td>
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<tr>
<td>Decreased sodium</td>
<td>25</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>19</td>
</tr>
</tbody>
</table>

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 a 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 other studies described below with the incidence of antibodies in other studies or to other sacituzumab govitecan products may be misleading.

The analysis of immunogenicity of TRODELVY in serum samples from 106 patients with mTNBC was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-sacituzumab govitecan-hziy antibodies. Detection of the anti-sacituzumab govitecan-hziy antibodies was done using a 3-tier approach: screens, confirm, and titers. Persistent anti-sacituzumab govitecan-hziy antibodies developed in 2% (2/106) of patients.

DRUG INTERACTIONS

Effect of Other Drugs on TRODELVY

UGT1A1 Inducers

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 (see Warnings and Precautions). Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers (see Warnings and Precautions). Avoid administering UGT1A1 inducers with TRODELVY.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

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

Data

Animal data

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan-hziy.

Lactation

Risk Summary

There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 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, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Contraception

Females

TRODELVY can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Infertility

Females

Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential.

Pediatric Use

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

Geriatric Use

Of the patients who received TRODELVY, 19/108 (18%) patients with mTNBC and 144/408 (35%) of all patients were ≥ 65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.
Tisotumab Vedotin Holds Potential in Metastatic Cervical Cancer

by GINA MAURO

TISOTUMAB VEDOTIN DEMONSTRATED an objective response rate (ORR) of 24% (95% CI, 15.9%-33.3%) in patients with recurrent and/or metastatic cervical cancer who previously received doublet chemotherapy and bevacizumab (Avastin), according to phase 2 findings of the single-arm innovaTV 204 trial presented at the European Society for Medical Oncology Virtual Congress 2020.1

The ORR, assessed via an independent imaging review committee (IRC), comprised a 7% complete response rate and a 17% partial response rate, and the median duration of response (DOR) was 8.3 months (95% CI, 4.2-not reached). Most responses were rapid, with a median time to response (TTR) of 1.4 months (range, 1.1-5.1), and activity was observed within the first 2 treatment cycles, Robert L. Coleman, MD, the lead study author, said in a presentation during the meeting (TABLE).1

Coleman, a 2020 Giants of Cancer Care® award winner, is chief scientific officer of The US Oncology Network.

“Tisotumab vedotin demonstrated compelling, rapid, and durable antitumor activity with encouraging PFS [progression-free survival] and OS [overall survival] in women with recurrent or metastatic cervical cancer previously treated with doublet chemotherapy, with bevacizumab, if eligible,” said Coleman. “Results from this study suggest that tisotumab vedotin has the potential to be a new therapy for patients with previously treated recurrent and/or metastatic cervical cancer.”

Recurrent and/or metastatic cervical cancer remains a significant cause of mortality in women, Coleman explained, adding that there is a high unmet need following resistance to or progression on standard frontline paclitaxel with platinum/topotecan with bevacizumab, if eligible. Currently, no established second-line standard-of-care option exists for these patients. Cytotoxic therapy, given as monotherapy, is found to have a poor benefit/risk profile with limited activity; although pembrolizumab (Keytruda) is available for patients with PD-L1-positive cervical cancer, the ORR with the agent is just 14.3%, as reported in the phase 2 KEYNOTE-158 study (NCT02628067).2

Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and covalently linked to monomethyl auristatin E, a microtubule-disrupting agent, via a protease-cleavable linker. TF is known to be highly prevalent in cervical cancer and other solid tumors and is associated with cancer pathophysiology and poor prognosis. Additionally, it is co-opted by tumor cells to promote tumor growth, angiogenesis, and metastasis.

In normal physiology, the primary role of TF is to initiate the coagulation cascade following vascular injury. The direct cytotoxicity associated with tisotumab vedotin may be augmented by the bystander effect and multiple immune-related effects, such as immunogenic cell death, antibody-directed cellular cytotoxicity, and antibody-dependent cellular phagocytosis, Coleman added.

Previously, results from a first-in-human trial demonstrated encouraging clinical activity with tisotumab vedotin, which Coleman added was shown to have multiple antitumor effects in cervical cancer in the innovaTV 201 trial.3

In the pivotal, single-arm, phase 2 innovaTV 204 trial (NCT03438396), 101 patients with previously treated recurrent and/or metastatic cervical cancer were given tisotumab vedotin at 2.0 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor responses were assessed using CT/MRI at baseline every 6 weeks for the first 30 weeks and every 12 weeks thereafter.

**TABLE.** Findings From the innovaTV 204 Trial1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tisotumab vedotin (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>4.2 (3.0-4.4)</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>30% (20.8-40.1)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>12.1 (9.6-13.9)</td>
</tr>
<tr>
<td>6-month OS rate (95% CI)</td>
<td>79% (69.3-85.6)</td>
</tr>
<tr>
<td><strong>Patient response</strong></td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>24% (15.9-33.3)</td>
</tr>
<tr>
<td>CR rate</td>
<td>7%</td>
</tr>
<tr>
<td>PR rate</td>
<td>17%</td>
</tr>
<tr>
<td>Stable disease rate</td>
<td>49%</td>
</tr>
<tr>
<td>Progressive disease rate</td>
<td>24%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4%</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>8.3 (4.2-NR)</td>
</tr>
<tr>
<td>Median TTR, months (range)</td>
<td>1.4 (1.1-5.1)</td>
</tr>
<tr>
<td>Percentage of patients with reduction in target lesions*</td>
<td>79%</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTR, time to response.

*In patients with ≥1 post-baseline scan.
To be eligible for enrollment, patients had recurrent or extrapelvic metastatic disease, progressed during or following doublet chemotherapy with bevacizumab, had received 2 or fewer prior systemic regimens, and had an ECOG performance status of 0 or 1. The primary end point of the trial was ORR per RECIST v1.1 criteria via IRC; secondary end points included investigator-assessed ORR per RECIST v1.1 criteria, OS, safety, and DOR, TTR, and PFS by both IRC and investigator. Exploratory end points were biomarkers and health-related quality of life.

The median age of participants was 50 years (range, 31-78), with 95% of patients being White; 2%, Asian; 1%, Black/African American; and 2%, listed as other. More than half (58%) of patients had an ECOG performance status of 0; 68% had squamous cell carcinoma, followed by adenocarcinoma (27%) and adenosquamous carcinoma (5%). Ninety-four percent of patients had extrapelvic metastatic disease at baseline.

A total 54% of patients had received prior cisplatin plus radiation therapy, which was not considered a systemic therapy; 70% had received 1 previous line of systemic therapy for recurrent/metastatic disease. Sixty-three percent of patients had prior bevacizumab plus doublet chemotherapy as frontline therapy, and 56% did not respond to their last systemic treatment. Coleman noted that 96% of patients’ tumors were positive for membrane TF expression, although that was not an eligibility requirement.

The median duration of treatment was 4.2 months (range, 1-16), with a median 6 doses (range 1-21) of tisotumab vedotin received, and a high dose intensity was observed (95.9%). Four patients had treatment ongoing, and the majority of patients discontinued therapy due to radiographic disease progression (65%), followed by adverse effects (AEs; 13%), clinical progression (8%), withdrawal of consent (5%), death (4%), and investigator decision (1%). Thirty-three percent of patients remain in follow-up for survival.

At a median follow-up of 10.0 months (range, 0.7-17.9), additional findings showed that 49% of patients achieved stable disease and 24% had progressive disease; 4% of patients were not evaluable, all via IRC. Moreover, target lesions were reduced in 79% of patients with 1 or more postbaseline scan.

Clinical meaningful responses were also observed regardless of tumor histology (squamous, 23%; nonsquamous, 25%), lines of prior therapy (1, 28%; 2, 13%), responses to prior systemic treatment (responded, 26%; did not respond, 21%), and whether they received frontline doublet chemotherapy with bevacizumab (yes, 19%; no, 32%).

“Of note, the ORR in patients with nonsquamous histology, 25%, and [in those] previously treated with bevacizumab, 19%, are encouraging, as only limited data currently exist in these populations,” Coleman said.

Moreover, responses to tisotumab vedotin were observed regardless of membrane TF expression level. Seventy-six of the 80 patients for whom TF expression data were available were also evaluable for response, and a similar distribution of TF expression was observed between the various response groups.

Additional results showed that the median PFS was 4.2 months and OS was 12.1 months with the approach. Moreover, the 6-month PFS and OS rates were 30% and 79%, respectively.

Regarding safety, tisotumab vedotin showcased a manageable and tolerable safety profile, with no new safety signals identified. The most common treatment-related AEs (TRAEs) with a 10% or higher incidence rate included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (24%), dry eye (23%), myalgia (15%), anemia (12%), asthenia (12%), arthralgia (12%), decreased appetite (11%), keratitis (11%), and pruritus (10%). Most of these were grade 1/2, but grade 3/4 TRAEs occurred in 28% of patients. Among the 4 patients who died, 1 was due to septic shock that was considered to be treatment related.

Coleman noted that prespecified AEs of interest with the agent, including ocular toxicity (grade 1/2, 52%; grade 3, 2%), bleeding (grade 1/2, 37%; grade 3, 2%) and peripheral neuropathy (grade 1/2, 26%; grade 3, 7%) were generally mild and effectively managed with the use of an eye care plan and dose modifications for the ocular toxicity and peripheral neuropathy, respectively.

Times to onset of ocular, bleeding, and peripheral neuropathy TRAEs were 1.4 months, 0.3 months, and 3.1 months, respectively. Eighty-six percent, 90%, and 21% of events resolved in 0.7 months, 0.5 months, and 0.6 months, respectively. The lower resolution rate with peripheral neuropathy could be attributed in part to the protocol-defined follow-up period for AEs of 30 days, Coleman concluded.

For a full list of references, see the article at https://bit.ly/2SC2HJR.
FINANCIAL CHALLENGES ARE nothing new to community-based oncology practices. In recent years, practices have faced increasing pressure from a variety of external factors, including declining reimbursements, increasing direct and indirect remuneration fees, and rising drug costs. However, in early spring 2020, as coronavirus disease 2019 (COVID-19) spread throughout the country, the financial challenges intensified.

During the first few months of the pandemic, new oncology patient visits dropped sharply, and most oncology practices experienced a reduction in new patient volume of more than 50%, according to a survey conducted by Flatiron. Although new patient visits have rebounded somewhat, industry data indicate that they are still down from their more typical levels in early February 2020.

The impact of COVID-19 has been felt deeply by community-based oncologists. According to an August 2020 Cardinal Health survey of more than 70 oncologists and urologists, more than 60% said the pandemic had an either “severe” or “moderate” negative effect on their professional life, and more than half said it had a moderate or severe negative impact on their income. The negative effect on income was largely attributed to cancellation of elective services and procedures and the shift from office-based visits to teledicine appointments (TABLE).

Some practices adapted remarkably well in the first few months, but sustained flexibility and focus will be needed as the virus continues to affect health care.

OPTIMIZING TELEMEDICINE SERVICES
The use of telemedicine visits skyrocketed in April and peaked in May. An IQVIA survey of oncologists and other specialists showed that just 9% of patient visits were conducted via telemedicine before the pandemic, but telemedicine visits rose to 51% during the pandemic period and are expected to remain at 21% after the pandemic ends, according to a US Department of Health and Human services report.

Looking toward the future, leading practices are viewing telemedicine as a tool to complement and augment other types of patient interactions. Follow-ups, appointments to address questions, and palliative care check-ins can be managed effectively through telemedicine on an ongoing basis. Some practice leaders have said they also see telemedicine as a tool to support value-based care. For example, a patient who is experiencing an adverse event could connect with their provider via telemedicine for guidance before going to the emergency department or hospital, which might help oncologists to reduce unnecessary high-cost interventions.

Other practice leaders see an opportunity to use telemedicine more broadly with advanced practice providers to provide patient services such as chemotherapy education, which may also contribute to lower practice costs.

MANAGING CLAIMS SUBMISSIONS IN A TIMELY MANNER
One of the best ways for practices to “future-proof” their financial operations is to avoid billing backlogs and reimbursement denials.
by ensuring that claims submission processes are consistently followed. The reality is that submitting “unclean” claims—those that lack information or National Drug Code numbers, have incorrect coding, or are for services that weren’t preauthorized—can dramatically slow down the reimbursement process or lead to denials.

Although unclean claims have long been the leading reason for claims denials, the submission of unclean claims by oncology practices rose in early spring 2020, when many practices began advising staff to work remotely or come into the office just a few days a week.

In addition, timeliness of claims submissions took a hit. According to Karen Kellogg, PharmD, director of practice consulting at VitalSource GPO, the average amount of time to submit Medicare B claims for some oncology practices jumped from 15 days before the height of the pandemic.

“Although submission times have returned to more normal levels, these trends still serve as a cautionary tale for practices. Even when working in normal practice environments with well-articulated claims submission processes, it can be easy for interruptions and increased workloads to get in the way of accurate claims submission. When clinicians and staff are working outside of their normal environments, with more distractions, it gets even easier to make mistakes and to fall behind,” Kellogg said.

Understanding these challenges, savvy practices are continually evaluating their claims submission processes, making sure staff receive adequate training to understand those processes, and assigning specific team members with double-checking all claims to ensure they are submitted without error—especially when staff are transitioning between working in the office and at home. Best practice processes include the following:

- Have staff members document patient visits in real time, as soon as a visit is completed or a medication is administered.
- Assign specific team members to serve as “scribes” whose sole purpose is to document this information during the visit.
- Ensure that nurses document medication start and stop time, total number of units administered, and total amount of unit waste so that the practice doesn’t leave any reimbursement dollars on the table.
- Overtly task at least 1 specific team member—who it’s a nurse manager, a reimbursement director, a lead biller or coder, or even a physician—with overarching responsibility for making sure that clean claims submission processes are followed.

Monitoring and analyzing reimbursement trends can also drive increased value for practices. At Southern Oncology Specialists, a group of North Carolina–based oncology practices, administrators found that data analytics tools are critical in helping to manage finances during the pandemic.

“For us, the challenge has been ensuring our operations stay consistent and predictable in a time of great change. Data is king; we can’t run our business without it. Every day, we look at our practice analytics tool for billing reconciliation so we can understand what is still outstanding and what actions we may need to take. If we didn’t have this mind-set and tools to support it, it would be very difficult to have visibility into the whole picture,” said Sarah Cowart, practice manager at Southern Oncology Specialists.

### MAXIMIZING THE BOTTOM LINE BY CONTROLLING INVENTORY

Another key strategy for improving a practice’s financial health during times of uncertainty: Optimize medication inventory and reduce waste by improving charge capture, clinical workloads, and day-to-day inventory levels.

By using a web-based inventory management platform for a “just in time” drug inventory—keeping on hand only the medications needed for patients on a given day—practices can help prevent cash flow from being tied up with unused medications sitting on a shelf.

During the current pandemic, when patient volumes are more unpredictable than normal, this may be particularly helpful.

Inventory management systems help reduce costs by notifying a practice when the least costly version of a medication wasn’t purchased and by providing alerts of opportunities to take advantage of drug rebates. They also help practices significantly improve charge capture for billable services. This documentation helps the practice avoid bearing the financial burden of the unused portion of that medication.

Without an automated inventory management system to collect this information, human error can lead practices to unfairly shoulder excessive costs related to billable waste. On average, monthly billable waste for a 4-site practice can range from $50,000 to $96,000 per site, according to aggregated VitalSource GPO data.

Amy Valley, PharmD, is vice president of clinical strategy and technology solutions at Cardinal Health Specialty Solutions.

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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 therapy1

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 the 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)\textsuperscript{1*}

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)\textsuperscript{1*}

\textbf{Median DoR: 21.7 months (range: 0, 24)\textsuperscript{1s}}

\textsuperscript{1s}Assessed by an Independent Review Committee.
\textsuperscript{1s}Kaplan-Meier estimates.

SAFETY PROFILE\textsuperscript{1}
- 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%).

\textbf{For more details on Adverse Reactions, refer to the full Prescribing Information.}

MONJUVI® (tfasitamab-cxix)

Initial U.S. Approval: 2020

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 (ASCIT).

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.

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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 (9%), 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 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 3: Adverse Reactions ≥10% in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MONJUVI (N=81)</th>
</tr>
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<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%), dizziness (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%)
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 increased</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</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-boosted 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 hematologic 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.

**Pregnancy Testing**

Refer to the prescribing information for lenalidomide for pregnancy testing requirements prior to initiating the combination of MONJUVI with lenalidomide.

**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.
Building Patient Engagement in Virtual Visit Era

by TODD SHRYOCK

THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic brought telehealth into the mainstream for many physicians and patients. Usage rates have declined from highs seen in the spring, but experts say that telehealth will play a much bigger role in health care moving forward and that physicians need to embrace it in order to succeed.

In this Q&A, Caroline Brennan, PhD, vice president of the health division of Escalent, a health care research firm, talks about telehealth strategies and trends.

Editor’s note: The transcript has been edited for clarity and brevity.

Q How can doctors encourage people to use telehealth for the first time?

A It’s really all about communication at every stage of that interaction between the patient, the office, and the doctor. The office can be offering telehealth as 1 of the options available to patients and provide a little bit of background about how that visit would work. Other ways that the doctors can improve that or to encourage usage of it is to have a lot of information on their website. This could include explaining how it works, not just the technological aspects of it, but what to expect, FAQs, or other things such as anonymized patient testimonials.

Q How much of the reluctance to use telehealth comes from not having a comfort level with the technology? And how can doctors help patients overcome that?

A What’s interesting is when we started our research on this, we thought that the technology barrier would be significant. And what we found is not that many people expressed concern about technology, about not being tech savvy, or not having some tools at home to have these telehealth visits. But nonetheless, anytime any of us go on a new website, log in, and use technology for the first time, there’s always some apprehension. What the doctors’ offices can do is provide very detailed login information, exactly what needs to be downloaded, how it’s going to work, maybe even provide some test runs, so that people can get more comfortable with it before they actually show up for that first appointment.

Q What are some best practices doctors should use during a telehealth visit?

A One thing that we did hear loud and clear is that people are very concerned about was the face-to-face interaction and missing out on that. Anything that the doctor can do to recreate it or simulate what an in-person visit would be like would go a long way in putting the patient at ease. Things such as small talk, eye contact with the patient, setting the expectations of how that visit might go for their particular medical condition or concern are important.

Q Why should doctors continue to use telehealth once the pandemic is over, considering that many of them are more comfortable with in-person visits?

A Everybody is probably more comfortable with in-person visits. We've realized that there are a lot of convenience factors here and it’s also opening up health care to people who might not be as apt to go to the doctor’s office. Maybe they're very busy, they don't have reliable transportation to get there, or maybe a doctor’s office is very far away, so it takes a lot of time. Continuing to offer telehealth as a robust alternative to the in-person visit would improve the opportunity for a lot of other people to get health care that they might not otherwise be accessing.

Q Telehealth usage rates have dropped from the initial highs in the spring. How can physicians encourage patients to keep using it when appropriate?

A It all comes down to bringing it up when they’re making the appointment, whether that’s actually on the phone or even if they’re booking the appointment online, offering that as an option. Word of mouth is very persuasive, so as people slowly get more experienced with it, and they tell their friends and family that no, it actually wasn’t so bad and that they had a good experience. I think that would also go a long way in encouraging people to continue using it.

Q Is there a patient demographic that prefers telehealth?

A We found in our study that people of all walks of life were using telehealth—all ages, all income levels, socioeconomic backgrounds. However, we did see that those who were seniors, or older folks, as well as those with lower incomes, were not using it quite at the same rate as others, which is interesting, especially for the seniors. They might be a particular group of people who would benefit from telehealth not just during COVID-19, but longer term, in terms of mitigating transportation concerns that they have, or if they have a lot of medical appointments.

Q What does the long-term future of telehealth look like in the United States?

A It is not going to replace in-person visits. But I do think it will remain as a viable option in a lot of cases for a lot of people. At first, for very specific conditions and situations. But I think telehealth is here to stay, and anything that will increase people’s access to health care is a win in my book.
Telehealth Is Here to Stay: Opportunities and Challenges for Cancer Care

by RYAN NGUYEN, DO; AND SHIKHA JAIN, MD, FACP

ONCOLOGY PRACTICES ACROSS THE United States have rapidly increased telehealth use in 2020 to mitigate the risk of coronavirus disease 2019 (COVID-19) to patients with cancer who are at particular risk of complications. The initial results from the COVID-19 and Cancer Consortium Registry cohort study (NCT04354701) showed a case-fatality rate of 13% (compared with 2.9% among the general population, according to the Johns Hopkins Coronavirus Resource Center) among patients with a history of cancer and COVID-19, with increased age, increasing comorbidities, worse performance status, and active cancer as independent risk factors for increased mortality. Not only do patients with cancer face higher risks of morbidity and mortality if they contract the virus, they also face the challenges that arise with the inevitable delays in anticancer therapy during recovery from COVID-19.

At the University of Illinois Cancer Center (UICC), we have seen a marked increase in the use of telehealth services from March 2, 2020, that continues as we enter month 6 of the COVID-19 pandemic. Shifting selected in-person clinic visits to telehealth has helped us both reduce patients’ exposure risks and protect health care providers and patients who require in-person care from additional exposures. As health systems across the nation begin shifting to “business as usual,” many cancer practices and their patients will continue to use telehealth as a risk-reduction tool to augment cancer care. However, careful attention is needed to address barriers to delivering high-quality medical care via telehealth.

REGULATORY RELIEF

In March 2020, the Centers for Medicare & Medicaid Services (CMS) released an interim final rule that reduced barriers to telehealth access as COVID-19 cases grew in the United States (FAST FACTS). Whereas CMS previously covered telehealth only when a patient was receiving care in a facility in a nonurban area or in an area in a health professional shortage, telehealth could not be delivered directly to a patient’s home prior to the pandemic. CMS also dropped the requirement for telehealth recipients to have a prior relationship with a health care professional, allowing physicians to conduct new patient consultations via telehealth. The loosening of Health Insurance Portability and Accountability Act regulatory requirements on telehealth technologies for providers acting in good faith also allowed physicians and their patients to use widely available commercial audiovisual platforms such as Zoom and Skype. Finally, CMS increased compensation for telehealth visits to match the fee schedule for in-person services.

TELEHEALTH BOOM

The loosening of regulatory requirements led to a boom in telehealth use across health care. Findings of a study of New York University urgent care visits showed a 135% increase in telehealth visits from March 2, 2020, to April 14, 2020. According to results of an April 2020 McKinsey & Company consumer survey, consumer adoption of telehealth jumped from 11% in 2019 to 46% in 2020. The burst in telehealth usage also led to an increase in patients who feel comfortable using telehealth, with 76% of survey respondents reporting they were “highly” or “moderately” likely to use telehealth going forward.

CHOOSING VISITS APPROPRIATE FOR TELEHEALTH

Successful implementation and integration of telehealth into cancer care requires identifying which in-person services can be rendered safely and effectively with this modality. The American Society of Clinical Oncology special report on cancer care during the COVID-19 pandemic identifies eligible telemedicine visit types: COVID-19–positive infections, nonurgent high-risk patient populations, and symptom management. At UICC, to ensure patients scheduled for telehealth visits are appropriate, our team triages clinic schedules 1 week in advance to allow patients time to adjust their schedules and arrange transportation. Although attending physicians determine which visits may be converted to telehealth encounters, patients with more urgent questions or clinical needs are always offered the option of in-person services. Our teams have found telehealth to be an effective means of communicating with patients regarding nonurgent matters, and patients often appreciate not having to commit the time and transportation resources for issues that can be addressed with a phone call.
CHALLENGES IN EQUITABLE TELEHEALTH DELIVERY
COVID-19 has further exposed disparities in access to care for vulnerable populations. Although opportunities exist for telehealth to address and improve upon inequities in the health care system, the rapid shift to telehealth services also has the potential to widen disparities in access to care. Accessibility to a stable phone or broadband connection can be a challenge in rural areas or for patients with limited income. Among Americans older than 65 years, who make up 18% of the American population and are most likely to need chronic disease management, just 55% to 60% own a smartphone or have home broadband access. Low-income individuals have lower rates of smartphone ownership (71%), home broadband access (59%), internet use (82%), and basic digital literacy (53%). Also limiting the effectiveness of telehealth is the comfort of both physician and patient with use of telehealth technologies and digital health literacy. In our experience, we have found most patients to be comfortable with telephone-only visits, with a minority comfortable consistently using audiovisual communication. Patient subgroups with known limited digital literacy and access include older adults, low socioeconomic status, limited health literacy, limited English proficiency, and racial and ethnic minorities.

Although many of the conversions from in-person visits to telehealth encounters are well intentioned and provide opportunities for more accessibility for certain populations, for patients with limited access to telehealth, we opt to prioritize a return to in-person visits. As we traverse this pandemic and nimbly adapt and implement effective strategies to provide exceptional patient care to all our patients, it is essential that we assess the risks and benefits of the transition to telehealth visits with the potential barriers and limitations that may unintentionally negatively affect our patients. Every effort should be made to reduce the risk of COVID-19 to our patients, but we must also take into consideration how to best deliver equitable medical care to our at-risk patient populations and whether that can be delivered effectively with telehealth.

REFERENCES

In an interview with OneLive®, Cuellar discusses the challenges of data extrapolation for biosimilars. Cuellar is the oncology resident director, clinical pharmacist, and team leader of the Ambulatory Pharmacy Services Department, as well as clinical professor of pharmacy practice at the College of Pharmacy at the University of Illinois.

MORE FROM University of Illinois

Concerns With Extrapolating Data for Biosimilars Remain Prevalent Among Oncologists

A KNOWLEDGE GAP remains among the health care community regarding the differences in the approval process for biosimilars compared with that of reference product. The oncology field is still trying to adapt to this paradigm shift, according to Sandra Cueller, PharmD, BCOP.

Unlike their biologic counterparts, which have data for each individual indication, data for a biosimilar approval can be extrapolated across tumor histologies. This has caused some hesitancy in the field of oncology, Cuellar said. Moreover, due to the complexity of the molecules, many have questioned the overall utility of biosimilars. To overcome this hurdle, Cuellar said to go “back to the basics” and gain an understanding how biosimilars are approved.

In an interview with OneLive®, Cuellar discusses the challenges of data extrapolation for biosimilars. Cuellar is the oncology resident director, clinical pharmacist, and team leader of the Ambulatory Pharmacy Services Department, as well as clinical professor of pharmacy practice at the College of Pharmacy at the University of Illinois.

NEW APPROACHES FOR TREATING

patients with HER2-positive metastatic breast cancer are showing signs of efficacy against brain metastases, generating excitement about the potential to make critical advances and sparking questions about optimal sequencing. A panel of up-and-coming oncologists provided their key clinical takeaways about data from several practice-changing trials during The Talk, a new OncLive® video program that features thought-provoking exchanges about practical oncology issues in a virtual format.

Moderator Sarah Sammons, MD, was joined for the roundtable by Julia M. Collins, MD, MPH; Kelly McCann, MD, PhD; and Laura Spring, MD. The conversation revolved around the primary and subgroup analysis of 3 studies, each of which included patients with brain metastases:

• HER2CLIMB (NCT02614794) evaluated tucatinib (Tukysa) in combination with trastuzumab (Herceptin) and capecitabine (Xeloda) for patients with advanced unresectable or metastatic HER2-positive breast cancer who have received 1 or more prior anti-HER2-based regimens in the metastatic setting.1,2

• DESTINY-Breast01 (NCT03248492) assessed fam-trastuzumab deruxtecan-nxki (Enhertu) in patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti–HER2-based regimens in the metastatic setting.3,4

• NALA (NCT01808573) assessed neratinib (Nerlynx) plus capecitabine in patients with metastatic HER2-positive breast cancer who received 2 or more prior anti–HER2-based regimens in the metastatic setting.5,6

SAMMONS A very hot topic this year is metastatic HER2-positive breast cancer. It’s been a really exciting year in this field, both for clinicians and certainly for our patients. We have 3 approvals for drugs in the advanced setting, and we finally put the importance on brain metastasis that they deserve.

So we’re first going to get started with the 3 FDA approvals: tucatinib, added to trastuzumab and capecitabine; trastuzumab deruxtecan; and neratinib plus capecitabine. Kelly, could you talk to us a little bit about the HER2CLIMB trial?

MCCANN Sure. I think tucatinib is one of the most exciting drugs to get FDA approval in the past year, mostly because the HER2CLIMB trial enrolled patients who had brain metastases that had not been treated. And those patients are typically excluded from clinical trials. So about half of their patients actually had brain metastases.

In our practice, approximately half of our patients with metastatic HER2-positive...
disease will eventually go on to develop brain metastases. So we really need more drugs that cross the blood-brain barrier.

HER2CLIMB was a large phase 2 trial that enrolled more than 600 patients with metastatic HER2-positive breast cancer to either tucatinib plus intravenous trastuzumab plus capecitabine, versus placebo plus trastuzumab plus capecitabine. Because so many patients had brain metastases, they were able to conduct a subgroup analysis.

In the overall population, the response rate was approximately 40% for patients who received tucatinib versus 23% in the control arm. Median progression-free survival [PFS] in these patients, half of whom had brain metastases, was 7.8 months with tucatinib versus 5.6 months with placebo. Overall survival [OS] was also improved: almost 22 months versus 17.4 months, respectively.

As we know with all of the tyrosine kinase inhibitors [TKIs], such as neratinib and lapatinib [Tykerb], they all have the adverse effect of diarrhea, which was also common with tucatinib. And, of course, the patients are at risk for palmar-plantar erythrodysesthesia syndrome, so they should also be monitored for hepatic toxicity.

For my practice, when I’m trying to decide what the next line should be after a first-line therapy—usually a taxane plus trastuzumab or plus pertuzumab [Perjeta]—I might actually consider doing a brain MRI at that point to guide my decision on where to go next. This regimen has been approved for the second-line setting, even though patients enrolled in the trial needed to have already had trastuzumab, pertuzumab, and ado-trastuzumab emtansine [T-DM1; Kadcyla] as well.

Unlike the previous trial we spoke about, this was a single-arm phase 2 trial. The results demonstrated an impressive objective response rate of 90.9%, and the median PFS was 16.4 months. Notably, this was a very heavily pretreated population—the median number of prior therapies was 6. I think these results were quite remarkable given that.

It’s also important to note that the prescribing information for this drug does include a boxed warning for interstitial lung disease [ILD], and fatal outcomes from ILD occurred in 2.6% of patients. I do think interstitial lung disease is now better understood, and I think clinicians are certainly keeping their eye out for this, so hopefully it will be recognized earlier.

Results of this study were presented at the same time as the HER2CLIMB study at the San Antonio Breast Cancer Symposium [in 2019]. So with approval of both of these treatments, there’s been a lot of discussion in the breast cancer community about which regimen to favor and when.

SAMMONS
That’s a really good point you bring up. I haven’t thought about doing a brain MRI on patients after they progress on the first-line setting. I think the most bang for the buck in this trial has certainly been looking at the CNS [central nervous system] end point and how the patients with brain metastases did.

But I think, most importantly, is that the investigators in this trial showed us what we need to do with brain end points from now on in phase 3 randomized trials for HER2-positive advanced metastatic breast cancer. We just can’t plan a phase 3 trial without being really thoughtful about intracranial end points, and I think this will be an example for us moving forward.

DESTINY-BREAST01
SAMMONS
So the next compound that I think blew everyone away is trastuzumab deruxtecan. Laura, would you mind telling us about the DESTINY-Breast01 study?

SPRING
Trastuzumab deruxtecan is an antibody-drug conjugate composed of an anti-HER2 antibody trastuzumab as a cleavable linker that then has a cytotoxic payload, which in this case is a topoisomerase 1 inhibitor.

The agent was granted accelerated approval by the FDA in December 2019 based on the DESTINY-Breast01 trial, which enrolled patients with unresectable or metastatic HER2-positive breast cancer who had received 2 or more prior anti-HER2-based regimens in the metastatic setting. All patients had received ado-trastuzumab emtansine [T-DM1; Kadcyla] as well.

Unlike the previous trial we spoke about, this was a single-arm phase 2 trial. The results demonstrated an impressive objective response rate of 60.9%, and the median PFS was 16.4 months. Notably, this was a very heavily pretreated population—the median number of prior therapies was 6. I think these results were quite remarkable given that.

It’s also important to note that the prescribing information for this drug does include a boxed warning for interstitial lung disease [ILD], and fatal outcomes from ILD occurred in 2.6% of patients. I do think interstitial lung disease is now better understood, and I think clinicians are certainly keeping their eye out for this, so hopefully it will be recognized earlier.

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SAMMONS
I know my jaw hit the floor when I saw the waterfall plot for this drug. I mean we just haven’t seen anything like this in a patient with a medium of 6 lines of therapy. I know we’re young-career oncologists, but I don’t ever remember a waterfall plot like that in advanced breast cancer.

The other thing I thought was interesting is a patient on that trial had 27 lines of therapies. And I was thinking, ‘What are the possible 27 lines of therapy that a patient could have had?’ That’s amazing.

MCCANN
I think what’s really interesting about the payload is that it is a topoisomerase 1 inhibitor, and we don’t usually give those to our patients; we’re not giving irinotecan to patients with breast cancer.

The other thing I consider when I’m talking to patients is the tolerability of T-DM1. With this drug [trastuzumab deruxtecan], they could have thinning and experience more of the adverse effects of a drug like irinotecan probably because the payload diffuses outside of the cell.

SPRING
Yes, it almost makes it look like it’s more chemotherapy, and you see more of those adverse effects.

SAMMONS
Counseling patients on toxic death is hard to do. I know that all patients come in asking me about this drug, and we’re giving a lot of it. We have a registration-like protocol where we conduct CTs and PFTs [pulmonary function tests] at baseline and then repeat that if a patient has any pulmonary symptoms.

I am excited to see data from the phase 3 trials as well and see how toxicity will play out because I think we need more information on who’s at risk for pneumonitis. But trastuzumab deruxtecan is an excellent option for our patients. We’ve seen chest wall disease just melt away after 2 doses. It’s a great option.

COLLINS
If you’re talking to patients about these 2 options, are you sequencing the HER2CLIMB regimen prior to trastuzumab deruxtecan?

SAMMONS
I think the way that I’m sequencing is pretty solely dependent on whether or not they have brain metastasis right now and certainly what agents they’ve had previously. And everybody wants to know how we’re all sequencing them. And I think—does it really matter?
Investigators randomized 621 patients 1:1, and the primary end point was investigator-assessed PFS with a coprimary end point of OS. The addition of neratinib to capecitabine did very modestly meet the primary end point of PFS but not of OS. The 6-month PFS rates were 47.2% versus 37.8% favoring neratinib versus lapatinib, and for 12 months they were 29% versus 15% favoring neratinib. Modest, but a small benefit to neratinib over lapatinib with capecitabine.

They also looked at an interesting end point, which was time to intervention for symptomatic CNS disease. And neratinib was slightly better, with an overall incidence of 22.8% versus 29%. The other very important thing to note is that neratinib with capecitabine had much higher grade 3 diarrhea than lapatinib plus capecitabine did at 24% versus 12%.

Kelly, you’re still using a decent amount of neratinib and capecitabine?

I am. And the way that I get patients adjusted to the drug is usually a dose escalation of neratinib instead of the heavy use of Imodium [for diarrhea]. I might start off with 120 mg for a week, and then go up to 160 mg, and then go to the full dose of 240 mg. And for whatever reason, that dose escalation ameliorates the diarrhea.

The same thing with capecitabine. That drug is difficult to tolerate and if somebody gets hand-foot syndrome early on, they’re probably going to quit the drug, so I start that at a lower dose and dose escalate as tolerated too.

**INTRACRANIAL IMPACT**

LET’S DIVE INTO THE SPECIFICS ON INTRACRANIAL EFFICACY OF ALL THESE AGENTS BECAUSE I THINK THAT’S REALLY HOW A LOT OF US ARE DETERMINING HOW WE’RE GOING TO CYCLE THEM IN THE CARE OF OUR PATIENTS. WE’LL START WITH THE HER2CLIMB STUDY. KELLY, CAN YOU TAKE US INTO THAT DATA?

In HER2CLIMB half the patients had brain metastases, and they were subcategorized as untreated or treated and stable, or treated and progressing. This was certainly a patient population that was at high risk for death. For patients with brain metastases, the median PFS was essentially the same.
as the overall population. Even though the median PFS and OS do not look like these giant numbers that are very impressive, the patient population was so high risk for bad outcomes that I think this is pretty impressive.

Investigators also analyzed median CNS PFS. In the tucatinib arm, the median CNS PFS is almost 10 months versus approximately 4 months in the control arm. The patients with brain metastases also had a better OS with tucatinib, 18 months versus 12 months.

**SAMMONS** I think a 6-month improvement in terms of intracranial PFS is really significant. That’s where there is a lot of morbidity with brain metastasis, and so to be able to prolong their intracranial progression I think is really important—so much so that because the approved indication for tucatinib is after 1 line of therapy, a lot of patients with brain metastases are skipping T-DM1 and going to this regimen. What are your thoughts on that?

**COLLINS** That’s been a hot topic at most institutions lately. I have trouble skipping the T-DM1 right now in that the data for these patients are post-THP [docetaxel, trastuzumab, and pertuzumab] and then T-DM1. I have been reserving this for third line based on the study. But since it has been approved in the second line, I wouldn’t say it’s wrong by any means, but I think it leaves us with a data-free zone to figure out when to sequence in the T-DM1.

**SPRING** It’s also showing the importance of multidisciplinary discussions with radiation oncology. If you have someone who got very good local therapy of their CNS disease or perhaps they had a few spots and had SRS [stereotactic radiosurgery], you may feel more comfortable with T-DM1 versus in a patient who had very widespread disease. Thinking about where local therapy fits in has been a factor that we try to consider.

**SAMMONS** I think the only patients at my institution for whom we consider skipping T-DM1 and going right to the HER2CLIMB regimen are those patients who have progressive brain metastases. These are patients who have had SRS or they’ve had a whole brain radiotherapy, and they had a progressive lesion. We have the best data to support this regimen for progressive brain metastases, which is not typically included in a phase 3 randomized design.

**MCCANN** HER2CLIMB was an exciting trial for me at San Antonio Breast because these drugs are so desperately needed. It’s easy to also go directly to trastuzumab deruxtecan and say this is an excellent, excellent drug, but they didn’t have many patients with CNS.

**SAMMONS** I think we all know that tucatinib with capecitabine and trastuzumab has very good intracranial efficacy and control. So the way we’re sequencing these drugs is kind of dependent on the brain metastasis.

What do we know about intracranial efficacy and the population with brain metastases from DESTINY-Breast01? There was a subgroup analysis of the DESTINY-Breast01 trial that looked at patients with CNS metastases at baseline as well as CNS status upon disease progression in the overall population. At the 5.4 mg/kg dose, only 24 of the 184 patients had CNS metastases at baseline.

It was good to see efficacy in the CNS subgroup. The direct-to-response rate was 58.3%, and the median PFS was 18.1 months, which was consistent with the overall population. But compared to something like a small molecule inhibitor like tucatinib, we know this is a much larger drug, an antibody-drug conjugate. And so, similar to T-DM1, trastuzumab deruxtecan likely cannot easily penetrate the CNS, and I don’t think we have a great understanding of why. In some cases we do see activity. I think this is another area that needs a lot more study.

**SAMMONS** The data showed that patients with stable brain metastases did just as well extracranially as the patients who didn’t have known metastases, but DESTINY-Breast01 did not require a baseline MRI or serial MRIs.

**SPRING** Only a subset of patients had that follow-up MRI, and investigators reported data at a median follow-up of 11.1 months for progression involving the brain, which occurred in 4 of 48 patients assessed for that, including 2 of 8 who had the baseline CNS metastases. It’s hard to draw a lot of conclusions from this subgroup analysis.

**SAMMONS** I would love to have some perspective or registrational studies on what the true intracranial efficacy is. I think at this point I certainly wouldn’t plan to put a patient with progressive brain metastases or patients who have brain metastases without local therapy, unless it was very tiny, on this compound.

An important thing to look for in future trials and the trials that we have is the differences between intracranial PFS and extracranial PFS, and how we manage both of them simultaneously and effectively. That’s always a challenge in designing trials for brain metastases and certainly in the clinic in treating these patients.
Analysis Reveals Efficacy Signals of PD-1 Inhibition in RCC

by JESSICA HERGERT

FINDINGS FROM A POOLED analysis of 3 clinical trials studying the interplay of immunophenotypes, somatic mutations, and chromosomal alterations on treatment efficacy in advanced renal cell carcinoma (RCC) shed light on the immunogenomic determinants of therapeutic response and survival while illuminating directions for future investigations.

“We are moving the needle forward with this research, but there is still a huge amount of work to do,” said first author David A. Braun, MD, PhD, who presented the results at the 2020 American Society of Clinical Oncology Virtual Scientific Program. “When we look at large genomic studies, we examine things in bulk. We take sections of a tumor, essentially grind [them] up in a blender to mix everything, and extract DNA and RNA to try to gain insight. However, these systems are complex and incredibly heterogeneous. Understanding what individual cell tumor and immune cell components drive response and resistance will be important, but it will also require moving beyond conventional genomic tools into more single-cell exploration.”

In an interview with OncologyLive®, Braun, a physician at Dana-Farber Cancer Institute and an instructor of medicine at Harvard Medical School, both in Boston, Massachusetts, discussed the findings from the analysis and the role of next-generation sequencing (NGS) in RCC, as well as priorities for drug development in the field.

Q What clinical questions were you seeking to address?

We know that immunotherapy and PD-1 blockade specifically have been transformative in the management of advanced RCC [in patients]. However, at the same time, we know that many patients do not achieve durable clinical benefit from these drugs. We don’t know what the determinants of response or resistance mechanisms are in this disease.

Although this has been explored in other cancer types, kidney cancer is different. Compared with melanoma or non–small cell lung cancer, RCC has a modest mutational burden. Also, in contrast with other cancer types, RCC has a robust CD8 T-cell infiltration. This standard hot versus cold paradigm of response/resistance typically doesn’t apply to RCC.

Knowing there is a clinical need to understand these factors and knowing we can’t necessarily extrapolate from other tumor types, we endeavored to investigate the immune or genomic determinants of response or resistance to PD-1 blockade [in RCC]. To do that, we worked as a large, collaborative group with a [substantial] cohort [of patients]. We took clinically annotated tumor specimens from patients who were enrolled in phase 1, phase 2, and phase 3 trials that evaluated the anti-PD-1 agent nivolumab [Opdivo]. The phase 1 trial was CheckMate 009 [NCT01358721], the phase 2 trial was CheckMate 010 [NCT01354431], and the randomized phase 3 trial was CheckMate 025 [NCT01668784]. Half the patients [in CheckMate 025] were treated with the mTOR inhibitor everolimus [Afinitor].

In total, we had 592 tumor specimens on which we could perform a mix of whole-exome sequencing to get mutations and copy number variants, as well as RNA sequencing to get gene expression patterns. We also performed an immunopathological analysis to visualize how many CD8 T cells were infiltrating the tumor, where they were spatially, and how this could [affect] response and resistance.

Q What methodology did your team use for this analysis?

First we looked to see what has been established in other tumor types to determine whether that paradigm works for clear cell RCC.
RCC. We examined several factors. There is a common belief that a high total mutational burden is a positive factor for PD-1 blockade because there are more targets for the immune system and more neoantigens that could be recognized. Therefore, we looked at those factors, which are better established in other cancer types. To our surprise, we found that total mutational burden, neoantigen load, or total number of copy number alterations did not have any impact on response or survival to PD-1 blockade. That did not seem to fit the picture for kidney cancer.

Understanding mechanisms of resistance, whether primary or innate...will be critical, as it will, hopefully, allow us to rationally design new therapies and combinations.”  
—DAVID A. BRAUN, MD, PHD

Next we examined whether individual genomic features existed that may be associated with response and resistance. We searched through the genome for all possible truncating mutations or loss-of-function mutations that were significantly recurring and had an impact on survival and response. In this pooled analysis, we found only 1: Loss-of-function mutations in PBRM1 were associated with improved response and survival to PD-1 blockade. We didn’t see that with mTOR inhibition.

A critical point is that these trials were all done in the post-antiangiogenic setting. All patients had advanced RCC, but they were all previously treated with something like a VEGF tyrosine kinase inhibitor, something that blocks angiogenesis. Then, after these patients progressed, they enrolled on this trial. In the context of other work on PBRM1, it appears that this effect of PBRM1 on response and survival does seem to be specific to the post-antiangiogenic setting. There is some interesting biology that probably underlies that.

After genomic features, we evaluated immune features; again, we looked at this paradigm of hot versus cold tumors. Moving beyond that, in other tumor types like bladder cancer, there is a third immune phenotype that has been described: immune excluded. [This means that] the T cells have marched up to the border of the tumor margin, but they are not able to penetrate the tumor center to have an effect. Up to 50% of bladder tumors have the immune- excluded phenotype, which accounts for a major source of resistance.

As part of this trial, we evaluated 219 tumors. We found that the immune- excluded phenotype, although prevalent in other cancer types, is not a prominent feature in kidney cancer. Only about 5% of those tumors were immune excluded, and in reality, the bulk of these tumors were very highly T cell infiltrating. Nearly 75% of tumors were highly infiltrated by CD8 T cells.

There is [the belief] that many CD8 T cells will lead to better response; however, in our case, having a high number of CD8 T cells infiltrating [the tumor had no effect] on response or survival compared with noninfiltrated tumors. This was perplexing to us, as this seemed to be a standard [understanding] of immune checkpoint inhibitors and response/resistance, but it doesn’t seem to be at play in RCC.

Next we wanted to determine whether any of these features integrate. Is there an interplay between genomic and immune features where we could miss the effect if we look at just 1 at a time? We looked at whether there were any genomic features between these hot, infiltrated tumors and the cold, noninfiltrated tumors.

To our surprise, we found that the clinically favored PBRM1 mutations were highly enriched in the noninfiltrated tumors. In contrast, we found that the infiltrated tumors were enriched in a number of copy number variants. One in particular, deletion 9p21.3, was highly enriched in infiltrated tumors [and] is associated with a much worse survival in response to PD-1 blockade.

As such, we see this potential interplay of immune and genomic features where, in theory, it looks as though the tumors with many T cells are poised to respond and the ones with low T cells aren’t. However, the tumors with low T cells are being pulled up by having more of these clinically favorable PBRM1 mutations, whereas the infiltrated tumors are being dragged down by having more than 1 of these deleterious 9p21.3 mutations.

We don’t see an effect when we look at 1 feature at a time, which is an important finding. This needs to be validated in other clinical data sets, but I hope this provides some conceptual framework for how to approach these response/resistance questions that, in a complex system, may not make sense. We have to learn how to integrate multiple features to see how they affect response/resistance.

Could evaluating the immunogenomic determinants of response and survival in other settings be beneficial?

All these trials were done in the post-antiangiogenic setting. The CheckMate 025 trial led to the approval of nivolumab in the second-line setting of RCC. We know that the field has moved at an incredible pace over the past few years, which is wonderful for our patients. Now PD-1 blockade is in the first-line setting alone and in combination with other therapies. The standard of care is PD-1 blockade combined with either another checkpoint inhibitor such as ipilimumab [Yervoy] or PD-1/PD-L1 blockade together with an antiangiogenic drug. Obviously, those are different clinical situations. There is the difference of second-line therapy compared with first-line therapy and the difference of monotherapy versus combination therapy.

This is an interesting finding that hints at some underlying biology and provides some framework; however, ultimately, I want this to be very useful to our patients. For that to be the case, we have to explore these findings in the first-line setting, where those drugs are now the standard of care.

Should NGS be conducted in all patients with RCC?

It is a great question, and it touches on how NGS affects the individual patient. I want to be very up front because when I see patients with kidney cancer, I like to provide them with more information rather than less. As such, I tend to favor genomic sequencing.
However, there are some big caveats to that. One is that the number of targetable mutations in kidney cancer is almost nonexistent. There are specific situations where a mutation may lend itself to enrollment in a clinical trial in a later line of therapy but not much that guides up-front therapy. As much as these explorations have helped move the needle forward in our understanding of response/resistance, none of these are usable biomarkers today. We are not in a situation where if a patient has a genomic feature, I know they should get therapy X versus another patient who has a different genomic feature. That is a difficult but important area to develop; we are definitely not there yet in terms of biomarkers.

I am always up front with my patients. I say, “The chance of this having an enormous benefit for you individually is low, maybe not 0, but it is low.” However, I hope that by incorporating NGS [into the treatment continuum for] more patients, we will gain an understanding so that the patient who walks into my office in 5 years will have a better comprehensive understanding of the genomic features of response/resistance that will enable us to improve outcomes.

Q How do emerging triplet regimens fit into the RCC paradigm?

It is incredibly exciting to see how fast the field has evolved. I’ve seen patients who had retired from medicine or urology. When they heard they had a diagnosis of kidney cancer, they were devastated because they remembered nothing was available. Now I can honestly say to my patients that this field is evolving so quickly that there has been an approval each year for the past few years. We saw nivolumab plus ipilimumab in 2018, we saw 2 PD-1/VEGF combinations in 2019, and it looks as if we are on course to see something similar, hopefully, in 2020.

Triplet therapy, if tolerated, has the potential to move the needle even further. However, some big questions remain. One is that we are talking about intensifying up-front therapy. However, a subset of patients may respond well to PD-1 blockade alone; that group will have durable, long-term survival with basic immunotherapy and should be spared the toxicity [that can come with] adding more therapies to its regimen.

Even as we add these therapies together and move up the curve, the patients who experience truly durable clinical benefit are still the minority. Understanding mechanisms of resistance, whether primary or innate resistance, or resistance acquired months or years later, will be critical, as it will, hopefully, allow us to rationally design new therapies and combinations to overcome these mechanisms.

Also, although this is incredibly exciting, we are using many of our best weapons in our arsenal up front. We would be using all our immune-based therapy in a triplet with our antiangiogenic agent. What is next? What do we do for the majority of patients who progress on antiangiogenic therapy and PD-1 blockade? To this end, several interesting [approaches] are being explored. For example, hypoxia-inducible factor 2α is an important target, and inhibiting it is a critical area of drug development. Other novel combinations are under exploration, as well, but what the appropriate treatment is post PD-1 treatment will be an important question.

Q What are the next steps for this research?

Having a good tumor microenvironment requires an interaction with a T cell that can recognize a target antigen on a tumor. We still know very little about that interaction. What are the effective tumor antigens in RCC? What T cells are capable of recognizing them? Those are open questions in this disease.

Hopefully, as we begin to answer these questions, that insight will pave the way to new therapies and antigens. Rather than giving broad immunotherapy, perhaps we can steer the immune system to target a specific tumor antigen. In the coming years, my hope is that this will serve as the first step in understanding the genomic and immune features of RCC and that we will continue to work toward a more comprehensive understanding [in that regard].

For a full list of references, see the article at https://bit.ly/30KPsel.
Join us to learn about SARCLISA (isatuximab-irfc)

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

Faculty information:

Joseph Mikhael, MD
Professor, Applied Cancer Research and Drug Discovery Division
Translational Genomics Research Institute, an affiliate of City of Hope Cancer Center
Chief Medical Officer
International Myeloma Foundation

Kenneth Shain, MD, PhD
Department of Malignant Hematology, Tumor Biology, and the Chemical Biology and Molecular Medicine Program
Moffitt Cancer Center
Assistant Professor
University of South Florida Morsani College of Medicine

In this iPub®, Drs. Joseph Mikhael and Kenneth Shain will:

- Discuss unmet needs in the treatment of relapsed refractory multiple myeloma
- Explore the mechanisms of SARCLISA, a treatment for relapsed refractory multiple myeloma
- Review clinical data and dosage and administration information for SARCLISA
- Answer questions about the clinical utility of SARCLISA and its role in the multiple myeloma treatment spectrum

Visit www.onclive.com/interactive-tools/sarclisa to watch the new iPub®.

Important Safety Information

CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS

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

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists,
Important Safety Information (cont.)

diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.

Neutropenia
SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

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

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

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

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

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

Please see brief summary of Prescribing Information on adjacent pages.

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MAT-US-201999 06/20
SARCLISA®
Rx Only
(iomatuzumab-irfc) injection, for intravenous use

Brief Summary of Prescribing Information

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer as an intravenous infusion over a period of 2 hours. Dose reductions for SARCLISA are recommended if patients develop infusion-related reactions. (See Warnings and Precautions (5.1)).

2.2 Recommended Premedications

Before the initial infusion of SARCLISA, administer a non–blood transfused, cross-matched ABO/RhD-compatible RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank policies. (See Drug Interactions (7.1)).

3 PRECAUTIONS

3.1 General Considerations

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

4 CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients. (See Warnings and Precautions (5.1)).

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Infusion-related reactions have been observed in 39% of patients treated with SARCLISA (see Adverse Reactions (2.1)). All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 96% of the cases. The most common signs and symptoms included dyspnea, cough, chills, and nausea. The most severe infusion reactions included hypotension, dyspnea, and fever. (See Adverse Reactions (6.1)).

5.2 Neutropenia

SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 86% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutrophil infections, defined as infection with concurrent grade 3–4 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutrophenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%). (See Adverse Reactions (6.1)).

5.3 Secondary Primary Malignancies

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected by serum protein electrophoresis and immunofixation assays used for the clinical monitoring of MM. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. (See Drug Interactions (7.1)).

5.4 Laboratory Test Interference

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-MM (N=257), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood typing samples administered without evidence of hemolysis, ABO/Rh typing was not affected by SARCLISA. Before the first SARCLISA infusion, conduct blood typing samples on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using unmodified treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank policies. (See Drug Interactions (7.1)).

5.5 Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bowel density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.3)). The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause fetal defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-related Reactions (see Warnings and Precautions (5.1)).
- Neutropenia (see Warnings and Precautions (5.2)).
- Secondary Primary Malignancies (see Warnings and Precautions (5.3)).

6.1 Clinical Trials Experience

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

The safety and efficacy of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/mm³, absolute neutrophil count ≥1 × 10⁹/L, creatinine density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.3)). The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause fetal defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

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The most common adverse reactions (≥20%) were neutropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea. Table 3 summarizes the adverse reactions in ICARIA-MM.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Pd) (N=149)</th>
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</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
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<tr>
<td><em>Pneumonia</em></td>
<td>31%</td>
<td>22%</td>
</tr>
<tr>
<td><em>Upper respiratory tract infection</em></td>
<td>57%</td>
<td>9%</td>
</tr>
<tr>
<td><em>Blood and lymphatic system disorders</em></td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td><em>Fatigue</em></td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td><em>Respiratory, thoracic and mediastinal disorders</em></td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Diarrhea</em></td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td><em>Nausea</em></td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td><em>Vomiting</em></td>
<td>12%</td>
<td>14%</td>
</tr>
</tbody>
</table>

CTCAE version 4.03

*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemorrhagic, pneumonia infected, pneumonia pneumococcal, pneumonia pneumatocele, pneumonia viral, candid pneumonia, pneumonia bacterial, hemorrhagic infection, lung infection, pneumonia fungal, and pneumonitis jiroveci pneumonia.

Upper respiratory tract infection includes bronchitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenza virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

Hypersensitivity reactions include dyspnea, dyspnea exertional, and dyspnea at rest.

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

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Parameter n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anergy</strong></td>
<td>151 (60)</td>
<td>145 (60)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>146 (50)</td>
<td>137 (50)</td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>140 (50)</td>
<td>137 (50)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>140 (50)</td>
<td>137 (50)</td>
</tr>
</tbody>
</table>

### Description of Selected Adverse Reactions

**Infusion-related reactions**

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 36 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 3.2%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypotension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to infusion interruption was 35 minutes.

In a separate study (TID 14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 40% of patients, at the first administration, of the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM. Infusions in ICARIA-MM, the incidence of Grade 3 or higher reactions was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 4.5% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.

### 6.2 Immuneinjury

As with all therapeutic proteins, there is a potential for immune response to antigen formation which is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies (including neutralizing antibodies) 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 isatuximab-irfc products may be misleading.

In ICARIA-MM, to patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent ASAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

### 7.1 Laboratory Test Interference

**Interference with Serological Testing**

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiplatelet tests (Indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatch in patients treated with SARCLISA (see Warnings and Precautions (5.4)).

**Interference with Serum Protein Electrophoresis and Immunophenotyping**

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on SARCLISA use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted and the estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

**Clinical Considerations**

**Immunofluorescence reactions**

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Refer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.

**SARCLISA**

(isatuximab-irfc) injection, for intravenous use

Data

**Ammal data**

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (responses, fetus-maternal immune tolerance (mice), and early embryonic development (mice)).

### 8.2 Lactation

There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. 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 SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

### 8.3 Females and Males of Reproductive Potential

**Pregnancy Testing**

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

**Contraception**

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

**Pediatric Use**

Safety and effectiveness in pediatric patients has not been established.

### 8.5 Geriatric Use

The total number of subjects in clinical studies of SARCLISA, 53% (338 patients) were 65 or over, while 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years and over and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### 10 OVERDOSAGE

There is no known specific antidote for SARCLISA overdose.

In the event of overdose of SARCLISA, monitor the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.

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Bridgewater, NJ 08807
A SANOFI COMPANY
U.S. License No. 1752
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ISA-BPLR-SA-MAR20 Revised: March 2020
Novel Strategies for Targeting the “Guardian of the Genome” Emerge

by JANE DE LARTIGUE, PhD

AS THE “GUARDIAN OF THE GENOME” and the most frequently mutated gene in human cancer, TP53 and the p53 tumor suppressor protein it encodes make a compelling therapeutic target with the potential for broad-based activity. But p53 presents a significant challenge for investigators, and the field is littered with clinical trial failures and abandoned drug development programs.1,2

This year was shaping up to be a landmark one for this intensively researched cancer drug target, with a hotly anticipated readout from a phase 3 trial of idasanutlin, a small molecule inhibitor of the p53-regulatory protein MDM2.3,4

However, results from the phase 3 MIRROS trial in patients with relapsed/refractory acute myeloid leukemia (AML) proved yet another disappointment5 for a field that has taken more than its fair share of blows over the decades.1,2

Nevertheless, investigators continue to push the boundaries of drug development in their efforts to develop novel p53-targeting agents and potential combinatorial strategies. Several companies are pursuing drugs that reactivate mutant forms of the p53 protein, restoring its tumor-suppressive properties.

One such agent, eprenetapopt (APR-246), received a breakthrough therapy designation in January 2020 for the treatment of patients with TP53-mutant myelodysplastic syndromes (MDS).6 Promising phase 2 data for the drug were highlighted at the 2019 American Society of Hematology Annual Meeting (ASH).7

GUARDIAN OF THE GENOME

Discovered more than 4 decades ago,4 the p53 protein is best known for its role as a transcription factor. Modulating the expression of multiple important genes positions p53 as a master regulator of a range of cellular processes, the most thoroughly studied being the DNA damage response.

Levels of p53 protein are generally low; however, in response to cellular stressors such as DNA damage, p53 is activated, accumulates in the nucleus, and induces the expression of genes that contain specific response elements. Among its targets are regulators of the cell cycle, DNA repair, and apoptosis, which allow the cell to pause cycling to repair damaged DNA or induce cell death if the damage is irreparable. In this way, p53 serves as a barrier to the genomic instability that fosters cancer development, earning it the nickname “guardian of the genome” (FIGURE).2,9-12

The p53 protein is composed of multiple functional domains: Two transactivation domains operate together and independently to mediate the transcription of p53 target genes, a proline-rich domain is implicated in p53-mediated inhibition of cell growth and stimulation of apoptosis, and a DNA-binding domain allows p53 to bind the promoters of target genes.2

In addition, p53 contains an oligomerization domain that enables it to form a homotetramer (required for transcription factor activity), a nuclear export signal, and an unstructured C-terminal domain that is targeted by posttranslational modifications that fine-tune p53’s activity.2

The activity of p53 is tightly controlled by other mechanisms, most notably by 2 negative

FIGURE. A Master Regulator of Cellular Processes at Work
regulators, MDM2 and MDM4. MDM2 is an E3 ubiquitin ligase that tags p53 with the small molecule ubiquitin, promoting the removal of p53 from the nucleus and targeting it for degradation by the proteasome.\(^1,2,9,11\)

Notably, the MDM2 gene is a transcriptional target of p53; thus, a negative feedback loop exists whereby p53 promotes the expression of its own negative regulator. MDM4 does not possess E3 ligase activity but interacts with MDM2 to promote ubiquitination of p53.\(^2\)

**BREACHED DEFENSES**

The importance of p53 as a tumor suppressor is reflected in reports that it is mutated in approximately half of all human cancers.\(^2,9,10,12\) Its prevalence varies widely across tumor types, reaching up to 95% in high-grade serous ovarian cancer (TABLE 1).\(^13\)

Somatic TP53 mutations are also extremely common in small cell lung cancer, pancreatic cancer, squamous cell carcinoma of the head and neck, and invasive breast cancer, particularly the triple-negative subtype.\(^14\)

Meanwhile, germline mutations in TP53 are associated with the rare Li-Fraumeni syndrome, in which individuals have an increased risk of developing cancer over the course of their lifetime.\(^11,12\)

Although many types of mutation have been identified in TP53, the vast majority occur within the DNA-binding domain, affecting p53’s ability to activate its target genes and leading to a loss of tumor-suppressive function.\(^2,12\)

Interestingly, unlike other tumor suppressor proteins, which are usually affected by deletion or nonsense mutations, most TP53 mutations result in a single amino acid substitution.\(^3\) These missense mutations are broadly classified into 1 of 2 types: either contact mutations that directly impede p53’s ability to bind target genes’ DNA or structural mutations that induce a conformational change in the p53 protein that affects its function.\(^2,10,12\)

Moreover, it is thought that the effect of mutant p53 on carcinogenesis may occur through more than just a passive loss of its tumor-suppressive capabilities. Mutant p53 can also affect wild-type p53 when both forms are present in the same cell. Unlike deletions or nonsense mutations, missense mutations allow the production of full-length (albeit defective) protein. This mutant p53 protein is capable of forming complexes with the wild-type protein that dampen the anti-tumor functions of the wild-type protein.\(^2,10,12\)

The mutant form also has been shown to acquire protumorigenic functions through interaction with other proteins that play a role in various cancer hallmarks.\(^2,10,12\)

Even in the absence of gene mutations, p53 function is often impaired in cancer cells. A major mechanism is through dysregulation of the MDM2 and MDM4 proteins, which are frequently overexpressed in various tumor types. Ultimately, the p53 pathway is thought to be nearly universally dysfunctional in human malignancies, making it an enticing therapeutic target.\(^2,11\)

For decades, investigators have sought to harness the p53 protein in drug development, but tumor suppressor proteins are notoriously difficult to target and require unconventional therapeutic strategies. A variety of methods are under investigation today, according to a search of ClinicalTrials.gov. These include vaccines and agents with targets that affect p53 functions. One of the most prevalent strategies involves targeting MDM2 protein activity and one of the most innovative seeks to reactivate p53 regulation (TABLE 2).

**MANY CANDIDATES FOR INHIBITING MDM2**

Among the earliest and most promising approaches to treating tumors without TP53 mutations was the attempt to block the interaction between p53 and its negative regulator MDM2. Targeting protein-protein interactions also holds challenges, but investigators identified a hydrophobic groove on the surface of MDM2 that offered a binding foothold.\(^2,12\)

The early 2000s saw the emergence of the nutlins, named after the Roche facility in Nutley, New Jersey, where they were discovered.\(^3\) The first to advance to clinical trials, RG7112, showed promise in phase 1 studies but was limited by the development of significant gastrointestinal (GI) and hematologic toxicities.\(^1,2,9\)

Idasanutlin is a more potent and selective nutlin analogue based on a different chemical scaffold.\(^1,3,9\) Data from phase 1/2 studies suggested that idasanutlin had clinical activity alone and in combination with other drugs in patients with AML,\(^1\) a cancer type in which p53 dysfunction is highly prevalent despite a comparatively low rate of TP53 mutations (5%-8% of newly diagnosed patients; 30%-40% of therapy-related AML).\(^16\)

Idasanutlin advanced to the phase 3 MIRROS trial, in which it was evaluated in combination with cytarabine compared with cytarabine alone in patients with relapsed/refractory AML fit for intensive salvage therapy (NCT02545283). However, the MIRROS study was terminated due to futility based on efficacy results at a planned interim analysis, according to an update posted in May 2020 on ClinicalTrials.gov.\(^4\)

The results of this analysis were presented at the virtual 25th European Hematology Association Congress in June 2020. A total of 447 patients were randomized 2:1 to receive idasanutlin 300 mg (or placebo) twice daily.
TABLE 2. Select Clinical Trials Evaluating p53-Targeting Drugs

<table>
<thead>
<tr>
<th>Agent/industry developer</th>
<th>Clinical setting (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>p53 reactivator</strong></td>
<td></td>
</tr>
<tr>
<td>Eprenetapopt (APR-246)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Aprea Therapeutics</td>
<td>* Azacitidine in TP53-mutant MDS (NCT03745716)*</td>
</tr>
<tr>
<td></td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>* Azacitidine in TP53-mutant AML or MDS following ASCT (NCT03931291)*</td>
</tr>
<tr>
<td></td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>* Brutinib or venetoclax in TP53-mutant R/R NHL (NCT04419389)*</td>
</tr>
<tr>
<td></td>
<td>* Pembrolizumab in advanced solid tumors (NCT04363938)*</td>
</tr>
<tr>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>* Venetoclax and azacitidine in TP53-mutant myeloid malignancies (NCT04214860)*</td>
</tr>
<tr>
<td><strong>MDM2 inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>ASTX295 Astex Pharmaceuticals</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>In advanced solid tumors (NCT03975387)</td>
</tr>
<tr>
<td><strong>Bi 907828</strong> (Boehringer Ingelheim)</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>In advanced solid tumors (NCT03449381)</td>
</tr>
<tr>
<td></td>
<td>+ BI 754091 (PD-1 antibody) and BI 754111 (LAG-3 antibody) in advanced solid tumors (NCT03964233)</td>
</tr>
<tr>
<td><strong>KRT-232</strong> (Kartos Therapeutics)</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>In MF that progressed after JAK inhibitor or ruxolitinib treatment (NCT03662126)</td>
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<tr>
<td></td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>+ Acalabrutinib in R/R DLBCL or CLL (NCT04502394)*</td>
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<tr>
<td></td>
<td>+ Ruxolitinib in MF with suboptimal response to ruxolitinib (NCT04485260)*</td>
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<tr>
<td></td>
<td>+ LDAC or decitabine in AML (NCT04113616)</td>
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<tr>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>In newly diagnosed or recurrent GBM (NCT03107780)</td>
</tr>
<tr>
<td></td>
<td>+ RT in soft tissue sarcoma (NCT03217266)</td>
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<tr>
<td></td>
<td>+ Decitabine in R/R or newly diagnosed AML (NCT03041688)</td>
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<tr>
<td></td>
<td>+ Chemotherapy in AML (NCT04190550)*</td>
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<tr>
<td></td>
<td>+ Carfilzomib, lenalidomide, and dexamethasone in R/R MM</td>
</tr>
<tr>
<td><strong>Milademetan</strong> (DS-3032b) Daichi Sankyo</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>In advanced solid tumors or lymphomas (NCT0317782)*</td>
</tr>
<tr>
<td></td>
<td>+ /- Azacitidine in AML or high-risk MDS (NCT03219326)*</td>
</tr>
<tr>
<td><strong>APG-115</strong> Ascentage Pharma</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>In metastatic melanoma or advanced solid tumors (NCT03611868)</td>
</tr>
<tr>
<td></td>
<td>+ /- Carboplatin in salivary gland carcinoma (NCT03781996)</td>
</tr>
<tr>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>+ /- Azacitidine in R/R AML (NCT03453839)*</td>
</tr>
<tr>
<td></td>
<td>+ Azacitidine or cytarabine in AML and MDS (NCT04275518)</td>
</tr>
<tr>
<td></td>
<td>+ /- APG-2575 (BCL-2 inhibitor) in T-PLL (NCT04663439)*</td>
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<tr>
<td><strong>Idasanutlin</strong> (RG7388) Roche</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>+ Chemotherapy or venetoclax in pediatric or young adult R/R acute leukemias or solid tumors (NCT04029668)</td>
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<tr>
<td></td>
<td>+ Atezolizumab in mCRC (Morphus-CRC; NCT03555149)</td>
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<tr>
<td></td>
<td>+ Ixazomib and dexamethasone in R/R MM (NCT02633059)*</td>
</tr>
<tr>
<td></td>
<td>+ Cytarabine and daunorubicin in newly diagnosed AML; idasanutlin monotherapy for maintenance of first complete remission (NCT03850535)*</td>
</tr>
<tr>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>+ Venetoclax in R/R AML ineligible for chemotherapy (NCT02670044)</td>
</tr>
<tr>
<td><strong>Dual MDM2/MDM4 inhibitor; &quot;stapled peptide&quot;</strong></td>
<td>Phase 1/2</td>
</tr>
<tr>
<td><strong>ALRN-6924</strong> Alicer Therapeutics</td>
<td>+ Paclitaxel in advanced, metastatic, or unresectable solid tumors (NCT03725436)</td>
</tr>
<tr>
<td></td>
<td>+ /- Cytarabine in pediatric R/R cancers (NCT03654716)</td>
</tr>
<tr>
<td><strong>WE1 inhibitor targeting cell cycle</strong></td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>Adavosertib (AZD1775) AstraZeneca</td>
<td>In recurrent TP53-mutant uterine serous carcinoma or carcinosarcoma (NCT03668340)</td>
</tr>
<tr>
<td></td>
<td>+ Paclitaxel in advanced TP53-mutant R/R gastric adenocarcinoma (NCT02448329)</td>
</tr>
</tbody>
</table>

AAML, acute myeloid leukemia; ASCIT, allogeneic stem cell transplant; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; GBM, glioblastoma; LDAC, low-dose cytarabine; mCRC, metastatic colorectal cancer; MDS, myelodysplastic syndromes; MF, myelofibrosis; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; RT, radiation therapy; T-PLL, T-cell prolymphocytic leukemia.

*Trial is ongoing but not actively recruiting participants.

**: Trial is not yet recruiting.
was administered at doses of 15, 30, 60, 120, 240, 300, 360, and 480 mg. There were 3 dose-limiting toxicities (DLTs): grade 3 neutropenia and grade 3 and 4 thrombocytopenia. The highest tolerated dose, 240 mg, was evaluated in dose expansion (n = 68). The most common treatment-related AEs (TRAEs) in the dose-expansion group were diarrhea, nausea, vomiting, fatigue, decreased appetite, and thrombocytopenia, mostly grade 1 or 2 in severity.

Per central evaluation, 4% of patients had unconfirmed PRs (including patients with well-differentiated liposarcoma, squamous cell carcinoma, and breast cancer), whereas most patients experienced stable disease (SD). KRT-232 also recently showed limited clinical activity in a phase 1 clinical trial in patients with relapsed/refractory AML (NCT02016729).

Ascentage Pharma is developing another MDM2 antagonist, APG-115, and a phase 1 study in patients with advanced solid tumors has been completed (NCT02935907). Among 28 patients, who had received a median of 4 prior lines of therapy and were treated with doses ranging from 10 to 300 mg for 21 days of 28-day cycles, 6 patients experienced SD after 2 cycles. The most common AEs included fatigue, nausea, vomiting, diarrhea, decreased appetite, dehydration, neutropenia, leukopenia, pain in extremity, and thrombocytopenia.

None of the MDM2 inhibitors under evaluation block MDM4 activity, and tumors overexpressing this protein would likely be resistant to these drugs. A dual inhibitor of both MDM2 and MDM4 is therefore desirable, and Aileron Therapeutics has a first-in-class drug, ALRN-6924, in clinical trials. In p53, a helical region binds to both MDM2 and MDM4, and ALRN-6924 is a stapled peptide, locked in a helical conformation that mimics this region. It is being evaluated in several ongoing phase 1 clinical trials.

Aileron is also exploring ALRN-6924 as a chemoprotectant. It is anticipated that ALRN-6924 will arrest the cell cycle in normal cells that express wild-type p53, but not in cancer cells with a TP53 mutation. Thus, treatment should limit the off-target toxicity of DNA-damaging chemotherapies that target rapidly proliferating cells.

**EPRENETAPOPT TAKES A NOVEL APPROACH**

One of the most exciting strategies for targeting cells that have TP53 mutations is reactivation of the mutant protein. The most widely investigated drugs are PRIMA-1 (p53 reactivation and induction of massive apoptosis) and its methylated derivative, eprenetapopt.

Both are prodrugs that are converted into an active metabolite, methylene quinuclidinone, which binds covalently to thiol groups in the core of the mutant p53 protein and causes it to undergo a conformational change, restoring wild-type activity. Eprenetapopt is more potent and has improved membrane permeability compared with PRIMA-1, and it has become the focus of ongoing clinical trials. It demonstrated anticancer activity and had a favorable safety profile in a range of preclinical cancer models, which led to the commencement of early-stage clinical testing. In a first-in-human study, eprenetapopt was reported to be safe and showed some activity in patients with hematologic malignancies (NCT00900614).

Patients with TP53-mutant MDS have a particularly poor prognosis, and new treatment options are needed. In a phase 1/2 study (NCT03072043), eprenetapopt was evaluated in combination with the hypomethylating agent azacitidine in patients with TP53-mutated MDS (NCT03745716), and Aprea Therapeutics recently reported that enrollment was complete, with topline results expected in late 2020.

Interim results of a French trial were also presented at the 2019 ASH meeting. Fifty-three patients (34 with MDS and 19 with AML, all higher risk and harboring TP53 mutations) were treated with 4500 mg of eprenetapopt on days 1 to 4 and azacitidine 75 mg/m² on days 4 to 10 of 28-day cycles. Among 16 patients evaluable for response, The ORR was 75%, including 56% CR and 19% bone marrow CR or SD with hematologic improvement. Common TRAEs were febrile neutropenia and neurological toxicities, the latter including ataxia, cognitive impairment, acute confusion, isolated dizzi- ness, and facial paresthesia.

Eprenetapopt also demonstrated activity in combination with carboplatin and pegylated liposomal doxorubicin in patients with high-grade serous ovarian cancer, a cancer type with a high prevalence of TP53 mutations, in the phase 1/2 PISARRO trial (NCT02098343).
Panelists Stress Importance of Putting Your Best Foot Forward in Advanced RCC

by CHRISTINA T. LOGUIDICE

MANY PATIENTS WITH EARLY-STAGE renal cell carcinoma (RCC) are cured, but the prognosis for those with advanced disease remains poor, with the 5-year survival ranging from 0% to 20%.1 Although the treatment armamentarium for advanced RCC has significantly expanded over the past few years, obtaining the best outcomes requires selecting the most efficacious treatment up front, as a substantial proportion of patients do not reach subsequent treatment lines.

During an OncLive Peer Exchange®, a panel of kidney cancer experts emphasized the importance of risk stratification for guiding treatment decisions and discussed the clinical trials that have shaped the front-line treatment recommendations from the National Comprehensive Cancer Network (NCCN) for advanced clear cell RCC. They shared their insights on how they select between these treatments to maximize their patients’ outcomes up front as well as on an exciting new combination therapy that is poised to add another powerful weapon to the treatment arsenal. “I know I have got to take that first best shot. If patients don’t tolerate something, then I can dial it back, but we may not get a chance to do some fantastic salvage regimen if they don’t get some disease reduction in this first-line setting,” moderator Daniel J. George, MD, said. “For these patients, making the first best decision is critical,” he emphasized.

RISK STRATIFICATION

Several validated risk-stratification models can be used in clinical practice to stratify patients with advanced RCC, including the International Metastatic RCC Database Consortium (IMDC) model and the Memorial Sloan Kettering Cancer Center (MSKCC) Motzer criteria (TABLE 1).2,3 “The IMDC criteria were initially validated in the context of the VEGF-targeted therapy era. Predating that were the MSKCC Motzer criteria that were validated in the cytokine era,” Rana R. McKay, MD, said.

The panelists emphasized the importance of using such tools for risk stratification in every patient with metastatic RCC. “When we talk with our colleagues in the community, they sometimes suggest that they might be using a gestalt impression of whether a patient is good risk, intermediate risk, or poor risk. Now that we understand the biological underpinnings of what good, intermediate, and poor is, I am sticking to the criteria more directly. I have to say, it’s been a long time since I’ve not staged a patient with IMDC risk characteristics,” Sumanta Kumar Pal, MD, said.

McKay explained that patients with favorable risk tend to have a higher expression of angiogenesis-related genes and may benefit from VEGF inhibition, whereas those with intermediate and poor risk tend to show a more upregulated immune signature. “The application of these risk stratifications is critically important not just in determining systemic therapy but in thinking about the role of cytoreductive nephrectomy,” she said.

Although the IMDC and MSKCC Motzer models give each risk factor equal weight (Table 1), Neeraj Agarwal, MD, said he pays most attention to time from
original localized kidney cancer and nephrectomy to time of onset of metastatic disease. “If a patient is developing metastatic disease within 4 or 5 months from nephrectomy, that’s a bad sign. If I see someone who is coming to me 8 years after their original nephrectomy, it’s a different disease,” he said. George concurred, noting that it is the only risk factor that “speaks to the natural history of the disease,” whereas the others may be attributable to a variety of other factors.

“There are a lot of factors that affect anemia. Even hypercalcemia could be due to dietary, sedentary, or other factors. Performance status is definitely affected by a lot of factors in the patient,” he said.

KEY CLINICAL TRIALS

SHAPING NCCN TREATMENT RECOMMENDATIONS

The panelists proceeded to discuss some of the NCCN recommended frontline treatments (TABLE 2), particularly how they decide whether to proceed with a VEGF receptor-tyrosine kinase inhibitor (TKI) alone or in combination with immunotherapy or with immunotherapy alone. VEGF/TKI plus immunotherapy options recommended by the NCCN include axitinib (Inlyta)/pembrolizumab (Keytruda), which the FDA approved in April 2019 based on data from the phase 3 KEYNOTE-426 study, and axitinib/avelumab (Bavencio), approved in May 2019 based on the phase 3 JAVELIN Renal 101 (NCT02684006) trial.3,4 The recommended immunotherapy is nivolumab (Opdivo)/ipilimumab (Yervoy), which the FDA approved in April 2018 for previously untreated patients with intermediate- or poor-risk advanced RCC based on data from the phase 3 CheckMate 214 (NCT02231749) trial.7 The NCCN’s preferred VEGF/TKI monotherapies include pazopanib (Votrient) or sunitinib (Sutent) for patients with favorable risk, and cabozantinib (Cabometyx) for those with intermediate or poor risk, with the latter recommendation based on the phase 2 CABOSUN (NCT01835158) study. Cabozantinib was approved in December 2017 as a first-line treatment for patients with advanced RCC, regardless of risk profile.8

KEYNOTE-426: Axitinib/Pembrolizumab

KEYNOTE-426 randomly assigned 861 patients who had not received systemic therapy for advanced RCC to receive pembrolizumab 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally twice daily (n = 432), or sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks off (n = 429).9 After a median follow-up of 12.8 months, an estimated 89.9% of patients in the combination therapy arm were still alive at 12 months compared with 78.3% in the sunitinib arm (HR for death, 0.53; 95% CI, 0.38-0.74; P < .0001). The median progression-free survival (PFS) was 15.1 months in the combination therapy arm and 11.1 months in the sunitinib arm (HR for progression or death, 0.69; 95% CI, 0.57-0.84; P < .001), whereas the objective response rate (ORR) was 59.3% and 35.7% in these cohorts, respectively (P < .001).

“You see a benefit in overall survival in the overarching cohort and certainly a benefit in response rate and progression-free survival across a stratum,” Pal said. The study included patients from all risk groups and those with and without PD-L1 expression.

JAVELIN Renal 101: Axitinib/Avelumab

JAVELIN Renal 101 randomly assigned 886 patients to receive avelumab 10 mg/kg intravenously every 2 weeks in combination with axitinib 5 mg orally twice daily (n = 442), or sunitinib 50 mg orally once daily for 4 weeks and then 2 weeks off (n = 444).10 The median PFS with the combination therapy was 13.8 months in both the overall study population and the subset of patients with PD-L1-positive tumors, whereas the median PFS with sunitinib was 7.2 months in the PD-L1-positive cohort (HR for disease progression or death, 0.61; 95% CI, 0.47-0.79; P < .001) and 8.4 months in the overall study population (HR, 0.69; 95% CI, 0.56-0.84; P < .001).10

“The study showed a benefit in progression-free survival across a stratum, but it failed to show an improvement, at least to date, in overall survival,” Pal said. Updated efficacy results from the second interim analysis of JAVELIN Renal 101 were published in August 2020.11 Although these showed continued statistically significant improvement in PFS with avelumab/axitinib over sunitinib, the OS data remained immature. The PD-L1-positive cohort had an HR of 0.828 (95% CI, 0.79

TABLE 1. IMDC and MSKCC Motzer Models in Risk Stratification of Metastatic RCC2,3

<table>
<thead>
<tr>
<th>Scoring*</th>
<th>Risk groups defined as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>favorable: 0 risk factors</td>
</tr>
<tr>
<td>&lt;1 year from time of diagnosis to systemic therapy</td>
<td>✔</td>
</tr>
<tr>
<td>Karnofsky Performance Status &lt; 80%</td>
<td>✔</td>
</tr>
<tr>
<td>Hemoglobin less than lower limit of normal (approximately 120 g/L or 12 g/L)</td>
<td>✔</td>
</tr>
<tr>
<td>Corrected calcium greater than upper limit of normala (approximately 8.5-10.2 mg/dL)</td>
<td>✔</td>
</tr>
<tr>
<td>Neutrophils greater than upper limit of normal (approximately 2.0-7.0 x 10³/L)</td>
<td>✔</td>
</tr>
<tr>
<td>Platelets &gt; upper limit of normal (approximately 150,000-400,000 cells/µL)</td>
<td>✔</td>
</tr>
<tr>
<td>Lactate dehydrogenase &gt; 1.5x upper limit of normal (normal, 140 U/L)</td>
<td>✔</td>
</tr>
</tbody>
</table>

IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma.

*Presence of each risk factor adds 1 point to the patient’s score.

aCalcium should be corrected for low albumin before scoring.
Of the patients in the immunotherapy arm, 425 were intermediate or poor risk and 125 were favorable risk, whereas in the sunitinib arm, 422 patients were intermediate or poor risk and 124 were favorable risk. After a median follow-up of 32.4 months, the immunotherapy combination continued to show superiority over sunitinib in OS among the intermediate- and poor-risk patients (median not reached vs 26.6 months [HR, 0.66; 95% CI, 0.54-0.86; P = .0001]) and among the intention-to-treat (ITT) patients (median not reached vs 37.9 months [HR, 0.71; 95% CI, 0.59-0.86; P = .0003]). Benefit in PFS and ORR was also reported across cohorts. More recently, follow-up to 42 months showed sustained superiority with nivolumab/ipilumumab across cohorts in OS and ORR compared with sunitinib.15

“A longer follow-up is always compelling for me, especially when I’m looking at the durability of complete response, which is the first thing that comes to my mind when I think about ipilimumab/nivolumab. A 42-month follow-up is a big deal, and it continues to reinforce that this regimen induces those durable complete responses,” Agarwal said.

Among the ITT population, a CR occurred in 11% of the immunotherapy-treated patients versus 2% of the sunitinib-treated patients, and in the intermediate- and poor-risk patients, CR occurred in 10% of immunotherapy-treated patients and 1% of the sunitinib-treated patients.15 When asked how he defines a CR, Agarwal said as long as he sees the dominant lesions decreasing in size by greater than 90%, he considers it a CR.

Long-term follow-up data from CheckMate 214 presented at the European Society for Medical Oncology Virtual Congress 2020 showed that in the ITT population, nivolumab plus ipilimumab continued to outperform sunitinib (HR, 0.69; 95% CI, 0.59-0.81). The doublet improved survival in patients with intermediate- or poor-risk disease (HR, 0.69; 95% CI, 0.54-0.78), and responses remained deep and durable regardless of IMDC risk-based prognosis.16

**CheckMate 214: Nivolumab/IPilimumab**

The extended follow-up of the CheckMate 214 trial included 1096 patients who were randomly assigned to receive nivolumab/ipilimumab (n = 550) or sunitinib (n = 546).14

**TABLE 2. NCCN-Recommended First-Line Therapy for RCC With Clear Cell Histology Based on Patient Risk Profile**

<table>
<thead>
<tr>
<th>Risk Profile</th>
<th>Favorable risk</th>
<th>Intermediate/poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimens</td>
<td>Axitinib + pembrolizumb</td>
<td>Axitinib + pembrolizumb (category 1)</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>Other recommended regimens</td>
<td>Ipilimumab + nivolumab</td>
<td>Axitinib + nivolumab (category 1)</td>
</tr>
<tr>
<td></td>
<td>Axitinib + avelumab</td>
<td>Cabozantinib (category 2B)</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib (category 2B)</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Useful in certain circumstances</td>
<td>Active surveillance</td>
<td>Axitinib (category 2B)</td>
</tr>
<tr>
<td></td>
<td>Axitinib (category 2B)</td>
<td>High-dose IL-2</td>
</tr>
<tr>
<td></td>
<td>High-dose IL-2</td>
<td>Temsirolimus</td>
</tr>
</tbody>
</table>

IL, interleukin; NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma.

*All recommendations are category 2A unless otherwise noted.

**Putting the Clinical Trial Data Into Practice**

The panelists proceeded to discuss the importance of using the best treatments up front.

“Some studies, like the IMDC data sets, reflect how just 50% of patients make it to second-line treatment. Those numbers may be a bit better...
in the context of VEGF and [immuno-therapy], but we just don’t know yet at this point. I would suggest that means you can’t save the best for last here; you’ve got to put your best foot forward right up front,” Pal said.

George concurred, noting that he is especially concerned there won’t be an opportunity for second-line treatment in the setting of symptomatic bone metastasis, high tumor burden, and disconcerting symptoms such as pain and weight loss, the latter of which he said is really muscle loss. “When you lose muscle, it makes everything that much tougher to tolerate and [limits your ability] to get to your second or third line of therapy,” he said.

In patients with intermediate or poor risk, Agarwal said he looks for the regimen that has the most curative potential for the patient, first considering the level of CR the regimen has shown in clinical trials and then the durability of those CRs. He noted that both axitinib/pembrolizumab and nivolumab/ipilimumab have demonstrated the highest level of CR thus far, with the nivolumab/ipilimumab regimen showing the greatest durability of response. “If you look at the durability of complete responses, it’s hard to beat the ipilimumab/nivolumab combination at this point. [With the 42-month follow-up, we are seeing that one-third of patients are maintaining the responses overall],” he said.

Agarwal said that favorable-risk patients are a bit more challenging to treat because there can be significant variation among them. He remarked that this population can include patients with a single metastatic nodule that is not active as well as patients with multiple sites of metastasis and relatively high disease burden but with normal lab findings. Subsequently, he bases his treatment approach on disease volume in these patients. For those with low disease volume, Agarwal said he prefers active surveillance because treatments may cause more harm than good in such patients. “For just 1 or 2 sites of metastasis that are slowly growing, and when the patient is otherwise doing well, it’s single-agent VEGF/TKI,“ he said. He said this can include pazopanib and sunitinib, but that he also considers the CABOSUN trial data. “Cabozantinib was superior to sunitinib, so I don’t hesitate to pick up cabozantinib as a VEGF/TKI of choice for these patients,” he said. In patients with more rapidly progressing disease, but who are still in the favorable-risk category, he tends to pick up axitinib/pembrolizumab.

Another important factor in treatment decision-making the panelists discussed is the need to account for patient factors, including age, fitness level, and goals. “You may have a favorable-risk patient who is young and healthy, and although they’re a favorable risk, you still may be swayed to use an IO/IO [immuno-oncology] combination for that individual. You may [also] have a poor-risk patient who may be older and doesn’t want to come in and get IV [intravenous] treatment; they live far away from the center, they have other comorbidities, and you’re going to say, ‘You know what, we’re just going to do cabozantinib for you based on the CABOSUN trial data,’ ” McKay said. She pointed out that although it is important to understand and apply clinical trial data, “there’s a lot of gray and art” in treatment decision-making.

**NEW REGIMEN ON THE HORIZON: NIVOLUMAB + CABOZANTINIB**

A new combination that has generated considerable excitement among the panelists is nivolumab plus cabozantinib, currently being studied in the phase 3 CheckMate 9ER trial (NCT03141177). Topline results showed that the combination not only significantly improved OS but also doubled PFS and response rates compared with sunitinib, prompting CheckMate 9ER to meet all efficacy endpoints. The OS, PFS, and ORR advantages were consistently seen across IMDC risk status, PD-L1 expression, and bone metastases.

Specifically, the doublet therapy reduced the risk of death or disease progression by 49%. The secondary end point of median overall survival was not reached in either arm, but risk of death was reduced by 40%. At a median follow-up of 10.6 months, the median OS was not reached in either treatment arm (HR, 0.60; 98.89% CI, 0.40-0.89; P = .0010). The median PFS, also evaluated at 10.6 months, was 16.6 months with the 2-drug approach versus 8.3 months with sunitinib HR, 0.51; 95% CI, 0.41-0.64; P < .0001). The ORR was 55.7% with nivolumab and cabozantinib and 27.1% with sunitinib.

“My sense was that, after bevacizumab/atezolizumab came out, all the VEGF/IO regimens to emerge thereafter would face an uphill battle. If you’re competing against sunitinib, you’re going to have more and more patients who get a VEGF inhibitor up front, cross over, and get second-line immunotherapy, then that would certainly make an overall survival bar even higher. Seeing CheckMate 9ER emerge with this impressive signal for OS and PFS advantage is incredible,” Pal said. He also said that he already has settings in which he would preferentially use this regimen, despite there not yet being substantial follow-up. “[I would use it] for those patients with bone metastasis and those patients with aggressive disease that were cast under the CABOSUN trial umbrella,” he said.

Based on the CheckMate 9ER data, a supplemental new drug application has been filed with the FDA for cabozantinib/nivolumab in patients with previously untreated advanced RCC. This is the first regulatory submission for cabozantinib in combination with an immune checkpoint inhibitor. ■
TGF-β and PD-L1 work together in the TME to promote tumor growth. Both PD-L1 and TGF-β drive immunosuppression leading to immune evasion. TGF-β stimulates angiogenesis, fibrosis, tumor cell motility, and metastasis. Targeting the TGF-β and PD-L1 pathways may limit immunosuppression and other mechanisms in the TME.