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International Liver Cancer Association

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BREAST CANCERS
Debu Tripathy, MD, on Evolving HER2+ Landscape

GYN MALIGNANCIES
Don S. Dizon, MD, on Discussing Sexual Health

DRUG SPOTLIGHT
LUNG CANCER
Justin F. Gainor, MD, Explains New RET-Targeting Drug

VANDERBILT-INGRAM CANCER CENTER
New Framework for Genetic Testing in Prostate Cancer Takes Shape
BY KERRY R. SCHAFFER, MD
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.

IN THIS iPub® DR. HOPE S. RUGO WILL

- Describe the TNBC disease state
- Understand the Prescribing Information for TRODELVY, including approved indication, warnings and precautions, adverse reactions, and other safety information
- Discuss the TRODELVY mechanism of action, appropriate patient populations, and clinical data
- Explain the dosage and administration of TRODELVY, premedication requirements, and recommendations for managing treatment-related adverse reactions

JOIN THIS MULTIDISCIPLINARY EXPERT:

Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology & Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

VIEW THE iPub® TODAY AT
OncLive.com/interactive-tools/mtnbc

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.
IMPORTANT SAFETY INFORMATION (cont.)

Contraindications
TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

Hypersensitivity
TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY. Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1% (6/408) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (3/408).

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting
TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively.

Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

Premedicate with a two or three drug combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade ≤1.

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

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.

Lactation

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.

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%).

Please see Brief Summary of full Prescribing Information on adjacent pages.
TRODELVY can cause severe or life-threatening neutropenia. 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 neutropenia may occur. 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. Without TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Febrile neutropenia occurred in 4% (24/408) patients treated with TRODELVY, including 9% (9/108) patients with mTNBC after at least two prior therapies. Less than 1% (1/408) 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.

Hypersensitivity

TRODELVY can cause severe or life-threatening hypersensitivity reactions. Anaphylactic reactions have been observed in clinical trials with TRODELVY.

Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with TRODELVY. Grade 3–4 hypersensitivity occurred in 1% (6/408) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (4/408).

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting

TRODELVY is emetogenic. Nausea occurred in 69% (274/408) of patients with mTNBC and 60% (251/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively. Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

Premedicate with a two or three-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CMV).

Withhold TRODELVY doses for Grade 3 nausea or Grade 3–4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade ≤ 1.

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the uridine diphosphate-glucuronosyltransferase 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% (103/395) 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, 3A-3H, 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 partners with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose [see Use in Specific Populations].

ADVERSE REACTIONS

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

- Neutropenia [see Warnings and Precautions]
- Diarrhea [see Warnings and Precautions]

ADVERSE REACTIONS were reported in 31% of the patients. The most frequent serious adverse reactions (reported in >1% of the patients receiving TRODELVY were febrile neutropenia (6%) vomiting (5%), anemia (5%), diarrhea (3%), rash (3%), nausea (2%), pyrexia (2%), and peripheral neuropathy (1%). TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to discontinuation were anaphylaxis, anorexia/fatigue, and headache (each <1%, 1 patient for each event). 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 (53%). 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/febrile neutropenia.

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

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse reaction</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>95</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Edema</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>74</td>
<td>17</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>64</td>
<td>43</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Dehydration</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
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<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

For a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant patients to discontinues TRODELVY and avoid pregnancy for at least 1 month prior to treatment with TRODELVY, during treatment, and for at least 1 month following the last dose of TRODELVY.

Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for the UGT1A1*28 allele is not established. TRODELVY is not recommended for patients with severe neutropenia. In patients who are homozygous for the UGT1A1*28 allele, TRODELVY is not recommended.

OVERDOSAGE

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.

Drug Interactions

Effect of Other Drugs on TRODELVY

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 it 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 to 4% and 15 to 20%, respectively.

Diarrhea

Advises patients of the risk of diarrhea. Instruct patients to immediately contact their healthcare provider if they experience diarrhea in the first 24 hours after treatment.

Infertility

Advises females of reproductive potential that TRODELVY may impair fertility [see Use in Specific Populations].

OVERDOSAGE

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.

Advises 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].

Psychiatric Disorders

Advises patients of the risk of psychiatric disorders. Instruct patients to immediately contact their healthcare provider if they experience suicidal ideation or behavior, severe depression, or other psychiatric disorders [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 symptoms such as dyspnea, pruritis, rash, flushing, or hypotension [see Warnings and Precautions].

Embryo-Fetal Toxicity

Advises female patients to contact their healthcare provider if they are pregnant or become pregnant. Instruct female patients of the risk of a fetus and potential loss of the pregnancy [see Use in Specific Populations].

Contraception

Advises female patients 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

Advises women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY [see Use in Specific Populations].

Infertility

Advises females of reproductive potential that TRODELVY may impair fertility [see Use in Specific Populations].

Manufactured by:
ImmunoGen, Inc.
300 The American Road
Morris Plains, NJ 07950, USA

See package insert for full Prescribing Information.
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 66.
Emotional AEs Remain a Blindspot in Oncology Care

Patients with cancer say they receive more help managing physical adverse effects (AEs) of therapy, such as nausea and vomiting, than they do for mental health AEs, such as anxiety and depression, according to the 2020 State of Cancer Survivorship Survey.
It’s Time to Celebrate the Giants

There’s always a sense of excitement in the air when we announce the OncLive® Giants of Cancer Care® award winners. For the past 8 years, this annual event is something that inspires our entire team at MJH Life Sciences®.

As a company dedicated to health care communications, we understand the complex nature of cancer care and the sacrifices that practicing oncologists and physician-scientists have made to advance the understanding of disease biology and improve outcomes for patients. We launched the Giants program with the inaugural 2013 class of honorees so that standouts in the oncology field would receive a measure of the recognition that our culture lavishes on sports and entertainment celebrities.

It is with great pleasure that we present the 2020 Giants of Cancer Care® award winners. Notably, the winners were chosen by a panel of prominent oncology leaders, including many previous Giants honorees.

This year’s class comprises 15 oncology specialists who have made significant contributions to improving care. In this issue of OncologyLive®, we capture some of the career highlights that prompted their selection for this award. These accomplishments cover a range of laboratory and translational achievements.

Some honorees embody both the discovery and the communication aspects of quality care. For example, Hope S. Rugo, MD, FASCO, is widely known not only for investigating novel strategies for treating patients with breast cancer and relieving adverse effects of therapy but also for sharing her knowledge at medical conferences and with patients. She was selected as the winner in the Education category.

Similarly, Clifford A. Hudis, MD, led clinical trials that helped change the breast cancer treatment paradigm before moving on to leadership posts at the American Society of Clinical Oncology. He won the Community Outreach award.

Others have played a less visible but no less impactful role in advancing cancer care. Olufunmilayo Falusi Olopade, MD, the honoree in the Genetics/Prevention category, won a MacArthur Foundation “genius grant” to pursue her studies of the molecular genetics of breast cancer in African and African American women. Laura J. van’t Veer, PhD, who won for Cancer Diagnostics, leverages information collected through big data projects to develop new tools for assessing patients for therapy.

In recognition of the collaborative nature of oncology research and practice, this year’s class of winners has a decidedly international flavor. Two of the honorees, Martine J. Piccart, MD, PhD, of Belgium, and Tony S. K. Mok, MD, of Hong Kong, are among the world’s best-known oncology leaders.

As with so many areas of our lives, the coronavirus disease 2019 pandemic has disrupted our plans to honor these eminent oncologists at a special reception and ceremony. However, we will feature the winners and their colleagues during an exciting broadcast that will air Thursday, November 5 at 7:30 pm EST during the 38th Annual CFS® conference.

We invite you to join us in honoring these Giants. To register for the virtual Giants of Cancer Care® awards ceremony, visit www.giantsofcancercare.com/rsvp. The presentation will be available on demand at www.giantsofcancercare.com after the event.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder
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

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.

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

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

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

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

Please see brief summary of Prescribing Information on adjacent pages.

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MAT-US-2019199 06/20
SARCLISA® [Rx Only]

2.1 Recommended Dosage

- Administer pre-infusion medications (see Dosage and Administration (2.2)).

- SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions if they occur (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)).

2.2 Recommended Premedications

Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions (see Warnings and Precautions (5.1)).

- Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥ 75 years of age).
- Acetaminophen 650 mg to 1000 mg orally (or equivalent).
- H2 antagonists.
- Diphenhydramine 25 mg to 50 mg orally or intravenously (or equivalent).

The intravenous route is preferred for at least the first 4 infusions.

2.3 Infusion Modifications

No dose reduction of SARCLISA is recommended. Dose delay may be required to allow recovery of blood counts in the event of hematologic toxicity (see Warnings and Precautions (5.1)).

For information concerning drugs given in combination with sarclisa, see manufacturer's prescribing information.

For drugs currently being administered with sarclisa, refer to the respective current prescribing information.

2.4 Preparation

Prepare the solution for infusion using aseptic technique as follows:

1. Calculate the dose (mg) of required sarclisa based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) (see Dosage and Administration (2.1)).
2. More than one sarclisa vial may be necessary to obtain the required dose for the patient.
3. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
4. Remove the volume of diluent from the 250 mL sodium chloride injection, USP, or 5% dextrose injection, USP/ dextrose injection, USP, diluent bag that is equal to the required volume of sarclisa injection.
5. Withdraw the necessary volume of sarclisa injection and add the required saline to the infusion bag of 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to achieve the appropriate sarclisa concentration for infusion.
6. The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) or P2-ethyl-ethylvinyl) (Ethene/PE) or ethyl vinyl acetate (EVA).
7. Gentle homogenize the diluted solution by inverting the bag.

2.5 Administration

- Administer the infusion solution by intravenous infusion using a non-bacterial tubing infusion set (in PE, PVC with or without DEHP, polybutadieene [PBD], or polyurethane [PU]), with a 0.22 micron in-line filter (polyethersulfone [PES], polyacrylonitrile, or cellulose acetate).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (see Table 2). Use prepared SARCLISA sarclisa solution in infusion sets 48 hours after stored refrigerated at 2°C–8°C, followed by 8 hours (including the infusion time) at room temperature, to administer SARCLISA solution concurrently in the same intravenous line with other agents.
- Infusion Rates

Infusion should be administered at a rate appropriate for the patient. Infusion rates are provided in the schedule in Table 1 (see Clinical Studies (14) in the full prescribing information).

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone

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

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

SARCLISA is used in combination with pomalidomide and dexamethasone.

Missed SARCLISA Doses

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

2.6 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 (6.1)). All infusion-related reactions started during the first sarclisa infusion and resolved on the same day in 86% of the cases. The most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe symptoms and signs included hypotension and dyspnea (see Adverse Reactions (6.1)). To decrease the risk and severity of infusion-related reactions, premedicate patients prior to sarclisa infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent; dexamethasone (see Dosage and Administration (2.2)). Monitor vital signs frequently during the entire sarclisa infusion. For patients with grade 1 or 2 reactions, interrupt sarclisa infusion and provide appropriate medical support. If symptoms improve, restart sarclisa infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion may be increased to the initial rate, and then increased incrementally, as shown in Table 2 (see Dosage and Administration (2.2)). In case symptoms do not improve post-interruption, permanently discontinue sarclisa and institute appropriate management.

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 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 (16%), lower respiratory tract (8%), and urinary tract (3%) (see Adverse Reactions (6.1)). 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 10⁹/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of sarclisa are recommended.

5.3 Second Primary Malignancies

Second primary malignancies were reported in 3% of patients in the sarclisa, pomalidomide and dexamethasone (Isa-Pd) arm and in 3.9% of patients in the pomalidomide and dexamethasone (Pd) arm, and included squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm) and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm) and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm).

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 patients, (5.1), 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/Rh typing was not affected by sarclisa treatment. Before the first sarclisa infusion, obtain a blood type and a cross-match for 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 dilution/neutralized RBCs. If an emergency transfusion is required, non-cross-matched ABO/Rh-compatible RBCs can be given as per local blood bank instructions.

5.5 Embryo-Fetal Toxicity

Based on its 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 (see Use in Specific Populations (8.1, 8.3)). The combination of sarclisa with pomalidomide is contraindicated in pregnant women because pomalidomide may cause 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)).
- Second 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 clinical 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 clearance ≥30 mL/min (MDRD formula), and AST and ALT ≤3 x ULN. Patients received sarclisa 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and low dose dexamethasone (Isa-Pd) (n=125) or pomalidomide and low dose dexamethasone (Pd) (n=149) (see Clinical Studies (14) in the full prescribing information). Among patients receiving Isa-Pd, 66% were exposed to sarclisa for 6 months or longer and 24% were exposed for greater than 12 months or longer. The median age of patients who received Isa-Pd was 68 years (range 36–83); 58% male, 76% white, and 14% Asian. Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in 5% of patients who received Isa-Pd included pulmonary edema (2%), upper respiratory tract infections (7%), and febrile neutropenia (1%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections (3%)). Permanent discontinuation due to adverse reaction (grades 1–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring discontinuation were infusion-related reactions (grades 1–4) in 7% of patients who received Isa-Pd (2%). In Isa-Pd, the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (2.6%). In addition, SARCLISA alone was discontinued in 3% of patients due to adverse reactions. Dose interruptions due to an adverse reaction occurred in 31% of patients who received Isa-Pd. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).
The most common adverse reactions (≥20%) were neutropenia, infection-related reactions, pneumonia, upper respiratory tract infection, and diarrhea. Table 3 summarizes the adverse reactions in ICARIA-MM.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (Grade 3)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Infection-related</td>
<td>38</td>
<td>1.3</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>31</td>
<td>2.2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>57</td>
<td>2.1</td>
</tr>
<tr>
<td>Blood and lymphoid system disorders</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>17</td>
<td>5.1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>20</td>
<td>1.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>20</td>
<td>4.0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>3.4</td>
</tr>
</tbody>
</table>

CTCAE version 4.03
*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophagocytic, pneumonia infiltrative, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemorrhagic infection, lung infection, pneumonia fungal, and pneumonitis jiroveci pneumonia.

Upper respiratory tract infection includes bronchiolitis, 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.

Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

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

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>151</td>
<td>46</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>146</td>
<td>37</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>140</td>
<td>64</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>148</td>
<td>64</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 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) 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 32.6%, 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 (TCI 14097 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, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

In ICARIA-MM, the incidence of Grade 3 or higher reactions was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 2% 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 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample 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 treatments including ICARIA-MM (N=564), the incidence of treatment emergent AGAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

### 7. DRUG INTERACTIONS

#### 7.1 Laboratory Test Interference

Interference with Serological Testing
SARCLISA, an anti-CDS8 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (Indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and anti-human globulin crossmatches in patients treated with SARCLISA (see Warnings and Precautions (5.4)).

Interference with Serum Protein Electrophoresis and Immunofixation
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

Pomalidomide may cause fetal harm when administered to a pregnant woman. 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 CDS8 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. 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. 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.

#### 8.2 Lactation

There are no available data on the presence of isatuximab-irfc in human milk. Milk composition, 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)). Therefore, advise female patients of reproductive potential to use an effective method of 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.

#### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### 8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 53% (338 patients) were 65 or over, while 14% (82 patients) were 75 or 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.
Technological Advances Come With a Cautionary Note

by MAURIE MARKMAN, MD

THE RECENT SENTENCING OF the Golden State Killer, an individual responsible for more than a dozen murders and 4 times as many rapes in California over many years, reminds us once again of the enormous potential for innovative technology to favorably transform our world while also raising a legitimate concern over how such advances may be employed for goals that would not be so positively viewed.1 The killer, whose wanton spree of violence began in 1975, was not captured until investigators using a DNA sample from a double murder in 1980 were ultimately able to find the suspect through a genealogy website where they identified a match to a distant relative.1 Although arguing that the result of this specific effort was inappropriate would be irrational, concern exists about the potential for individual privacy to be compromised if such technology were to be used for questionable purposes.

Similarly, in the realm of medicine, we see enormous opportunities for truly novel technologies to revolutionize the health and welfare of all members of society. A recent report revealed the essential equivalence of multichannel electrocardiogram readings obtained on a commercially available smartphone to those of a standard electrocardiogram, including for individuals with ST elevation and non-ST elevation myocardial infarctions.2 One can easily imagine the individual and societal impact of the potential for much earlier diagnosis of acute coronary syndromes as well as essential intervention following the development of a serious cardiac event.

POTENTIAL FOR ARTIFICIAL INTELLIGENCE

In the oncology arena, it is not difficult to find examples where rapidly proliferating artificial intelligence technology has transformed, or is on the verge of transforming, current management paradigms, particularly in the domain of cancer diagnostics. For example, a recent report of a novel system for the reading of breast cancer screening images revealed the rather impressive clinical utility of this artificial intelligence process.3 The specific algorithm was shown to be superior to 6 experienced radiologists who participated in this study and revealed a reduction in both false-positive and false-negative evaluations. Further, when a double-reading process (2 reviewers) was employed, the addition of the artificial intelligence platform resulted in an 88% reduction of the required effort of the second radiologist.

Similarly, a recent report of a “deep learning model” employing MRI of intratumoral and peritumoral regions of women undergoing radical surgery for cervical cancer revealed the benefits of this noninvasive approach in documenting lymph node involvement compared with standard MRI alone.4 Of note, the results of this imaging approach were shown to be highly prognostic for disease-free survival in this setting.

As a final brief example, investigators recently reported the development of a machine learning strategy that examined the molecular profiles of 7791 tumors involving 22 cancer types to determine whether these data could be helpful in the determination of the site of origin of a given malignancy.5 The algorithm was able to correctly diagnose the cancer in 73.8% of cases in this training set and in 74.1% of an independent group of 11,644 malignancies.5 In addition, in a group of 141 patients with a presumptive diagnosis of cancer of unknown primary site, the algorithm predicted the site of origin in 67.4% of the cases, suggesting the potential utility of this strategy in routine clinical pathology practice.
From the Editor

PITFALLS OF EARLY ADOPTION

However, we must acknowledge that we cannot always simply assume that the use of newer technology will be associated with a positive outcome. For example, dangers have recently been highlighted for the potential misuse of poorly constructed and considered race-adjusted algorithms designed to improve the quality of care that may result in the exact opposite outcome.

Similarly, the excessively early adoption of what may appear to be innovative device technology developed to improve surgical outcomes may actually compromise survival, as recently revealed for the use of minimally invasive radical surgical approaches in the management of early-stage cervical cancer. One wonders why the gynecologic oncology community so actively embraced the routine use of this strategy before phase 3 randomized trial data on the safety and benefits of this approach were available.

In this regard, it is somewhat ironic, and perhaps a bit disturbing, that the same issue of the *New England Journal of Medicine* that reported the results of such a phase 3 trial revealing the inferior survival of women randomized to minimally invasive radical surgery also included the results of a retrospective analysis of 1225 patients treated with this technique compared with a nonrandomized but carefully matched control group managed with an open surgical technique where reduced survival for the minimal invasive technique was also observed.

Although it would be pure speculation to estimate how many women might not have had their lives shortened if the results of a solidly evidence-based randomized trial had been reported before minimally invasive radical surgery for early-stage cervical cancer became routine in clinical practice, it would be quite appropriate to ask such a question with the goal of helping others avoid a serious technological misadventure in the cancer management arena in the future.

Advances in technology have a tremendous potential to improve both survival and quality of life for individuals with malignant disease, but all new approaches—regardless of their innovative nature—require an objective, rigorous assessment of their safety and clinical utility.

REFERENCES


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\textsuperscript{1-3}

**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 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**

**OVERALL POPULATION**

- **38%** REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH

**Median PFS:** 13.8 months with ZEJULA vs 8.2 months with placebo (HR 0.62; 95% CI 0.50-0.76) \(P<0.0001\)

**HRD POPULATION**

- **57%** REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH

**Median PFS:** 21.9 months with ZEJULA vs 10.4 months with placebo (HR 0.43; 95% CI 0.31-0.59) \(P<0.0001\)

**Study Design:** PRIMA, a randomized double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of once-daily ZEJULA versus placebo (2:1) in 733 women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to first-line platinum-based chemotherapy. The primary endpoint was a hierarchical calculation of PFS: first in patients with HRd tumors and then in all patients. PFS was measured from time of randomization to time of disease progression or death. At the time of PFS analysis, limited overall survival data were available with 11% deaths in the overall population.\(^1\,^4\)

**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 (56%), increased AST (35%) and increased ALT (29%).

**References:**


Visit ZEJULA.COM/HCP to explore the PRIMA data

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NRPJRNA200007 August 2020
Produced in USA.

Please see Brief Summary on the following pages.
Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 2). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.9) of full prescribing information).

5.3 Cardiovascular Effects

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

In PRIMA, Grade 4 hypertension occurred in 15% of ZEJULA-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 521 days) and with a median duration of 11 days (range: 1 to 61 days). There were no discontinuations due to hypotension.

In NOVA, Grade 3 hypertension occurred in 5% of ZEJULA-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in 1% of patients.

In QUADRA, Grade 3 hypertension occurred in 5% of ZEJULA-treated patients with a median time from first dose to first onset of 15 days (range: 1 to 118 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary (see Dosage and Administration (2.9) and Nonclinical Toxicology (13.2) of full prescribing information).

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology). ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the 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 patients who received ZEJULA in the pooled PRIMA, NOVA and QUADRA trials were nausea (65%), thrombocytopenia (65%), anemia (55%), fatigue (54%), constipation (19%), musculoskeletal pain (16%), abdominal pain (15%), vomiting (13%), neutropenia (12%), decreased appetite (12%), leukopenia (11%), insomnia (10%), headache (9%), medical event (9%), hypertension (9%), cough (8%), nasopharyngitis (8%), and urinary tract infection (8%).

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 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELUSA in PRIMA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELUSA</td>
</tr>
<tr>
<td></td>
<td>N=169</td>
</tr>
<tr>
<td>Decreased haemoglobin</td>
<td>37</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>73</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71</td>
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<td>Increased glucose</td>
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<tr>
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<td>Decreased lymphocytes</td>
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</tr>
<tr>
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<td>46</td>
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<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>36</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29</td>
</tr>
</tbody>
</table>

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

Among patients who received ZELUSA with the dose based on weight and platelet count, the median duration of treatment was 11.0 months (range: 1 day to 16 months).

Serious adverse reactions occurred in 27% of patients receiving ZELUSA. Serious adverse reactions in >2% of patients were anaemia (8%), thrombocytopenia (7%), and neutropenia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZELUSA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZELUSA included thrombocytopenia and anaemia (3.0% each), and neutropenia (2.4%).

Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anaemia (23%), and neutropenia (15%).

Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZELUSA.

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=169</td>
<td>N=244</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>37</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>36</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=169</td>
<td>N=244</td>
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<tr>
<td>Decreased hemoglobin</td>
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<td>Increased glucose</td>
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<td>46</td>
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<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>36</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELUSA monotherapy 800 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 anaemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZELUSA in these patients was 250 days.

Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZELUSA in NOVA.

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=367</td>
<td>N=179</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>85</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>72</td>
</tr>
<tr>
<td>Decreased WBC count</td>
<td>66</td>
</tr>
<tr>
<td>Decrease in AST</td>
<td>36</td>
</tr>
<tr>
<td>Decrease in ALT</td>
<td>28</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
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<td>36</td>
</tr>
<tr>
<td>Decrease in ALT</td>
<td>28</td>
</tr>
</tbody>
</table>

- N=number of patients. WBC=white blood cells. ALT=Alanine aminotransferase. AST=Aspartate aminotransferase.
- The following adverse reactions and laboratory abnormalities have been identified in 21 to <10% of the 167 patients receiving ZELUSA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood
Treatments of Advanced Ovarian Cancer after Three or More Chemotherapies

The safety of ZEJULA monotherapy 300 mg once daily has been studied in QUADRRA, a single-arm study in 468 patients with recurrent high-grade serous ovarian, fallopian tube, or peritoneal peritoneal cancers who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRRA 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 >4% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 4-4) occurred in 2% 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 (4%), anemia (2%), neutropenia (1%), nausea (1%), vomiting (1%), fatigue (1%), and abdominal pain (1%).

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZEJULA. 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 Disorders: hypersensitivity (including anaphylaxis)

Nervous System Disorders: posterior reversible encephalopathy syndrome (PRES)

Psychiatric Disorders: confusion, state of disorientation, hallucination, cognitive impairment

Respiratory, Thoracic, and Mediastinal Disorders: non-infectious pneumonitis

Skin and Subcutaneous Tissue Disorders: photosensitivity

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women (see Clinical Pharmacology (12.1) of full prescribing information). There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and embryofetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted in niraparib. Appropriate pregnant women of the potential risk to a fetus.

The 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% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZEJULA, advise lactating women not to breastfeed during treatment with ZEJULA and for 1 month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

ZEJULA can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.3)). A pregnancy test is recommended for females of reproductive potential prior to initiating ZEJULA treatment.

Contraception

Females

ZEJULA can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.3)).

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months following the last dose.

Infertility

Males

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

8.5 Geriatric Use

In QUADRRA, 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 cannot be ruled out.

8.6 Renal Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

Medications

Advise patients to contact their healthcare provider if they experience unusual 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 monitor 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 (5.3)).

Dispensing 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, not to take an extra dose to make up for the one that was missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole: ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to contact their healthcare provider if they are pregnant or become pregnant. Inform females patients of the risk to a fetus and potential loss of the pregnancy (see Warnings and Precautions (5.3)).

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)).

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Pralsetinib Scores Approval for RET+ NSCLC, Priority Review for RET+ Thyroid Cancer

Pralsetinib (Gavreto) has received an indication for adults with metastatic RET fusion–positive non–small cell lung cancer (NSCLC) as detected by an FDA-approved test, representing the second therapy specifically for patients with RET-altered cancers. The FDA concurrently approved the Oncomine Dx Target Test, developed by Thermo Fisher Scientific, as a companion diagnostic to identify patients who could be candidates for the therapy.

The NSCLC indication is based on efficacy data from the phase 1/2 ARROW study (NCT03037385), which demonstrated that pralsetinib elicited durable clinical responses in patients with RET fusion–positive disease. Responses were seen irrespective of whether or not patients had received prior treatment and occurred independently of RET fusion partner or central nervous system involvement.

The overall response rate was 57% (95% CI, 46%-68%), with a complete response rate of 5.7% in the 87 patients with NSCLC who received prior platinum-based chemotherapy. The median duration of response had not yet been reached (95% CI, 15.2 months–not reached). Among 27 treatment-naïve patients, the overall response rate was 70% (95% CI, 50%-86%), with an 11% complete response rate.

The FDA also granted pralsetinib a priority review for patients with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) and RET fusion–positive thyroid cancer. A decision is expected by February 28, 2021.

The regulatory filing also includes data from the ARROW trial for this patient population. The objective response rates were 74% and 60% in the 19 patients with RET-mutant MTC and the 53 patients who had previously received an approved multikinase inhibitor, respectively. In the 11 patients with RET fusion–positive thyroid cancer, the agent elicited an objective response rate of 91% (95% CI, 59%-100%), comprised entirely of partial responses.

In May 2020, the FDA approved selpercatinib (Retevmo), the first drug specifically targeted at patients with RET-altered cancers. It is indicated in RET fusion-positive NSCLC and thyroid cancer settings, and for RET-mutant MTC.

FDA OKs Expanded Use of Cytology Test in HPV+ Cervical Cancer

The next-generation CINtec PLUS Cytology test, which simultaneously detects p16 and Ki-67 to identify women whose human papillomavirus (HPV) infections are most likely to be associated with cervical precancers, is now approved for use in women who undergo cervical cancer screening and test positive for high-risk types of HPV. The expanded indication allows laboratories to use the test to triage positive results run on the cobas 6800/8800 systems in primary screening or cotesting programs.

When a cell expresses both p16 and Ki-67, it is highly likely that the patient has transforming HPV infections that can potentially progress to precancer or cancer. By identifying p16 and Ki-67, CINtec PLUS Cytology can help determine which women should be referred for immediate further diagnostic procedures, potentially preventing the development of advanced cervical disease, according to Roche, the assay’s developer.

The broadened utility of the assay builds on a March 11, 2020, approval as a companion diagnostic to identify patients who could be candidates for the therapy.

FDA Issues Alert For Safety, Efficacy of Atezolizumab/Paclitaxel in Breast Cancer

Following the IMpassion131 trial’s (NCT03125902) failure to demonstrate the effectiveness of atezolizumab (Tecentriq) plus paclitaxel in patients with treatment-naïve, inoperable locally advanced or metastatic triple-negative breast cancer (TNBC), the FDA issued an alert warning that paclitaxel should not be substituted for protein-bound paclitaxel in clinical practice.

The atezolizumb/paclitaxel combination did not show a statistically significant improvement in progression-free survival when used as a frontline treatment for patients with PD-L1–positive TNBC, causing the phase 3 study to miss its primary end point (HR, 0.82; 95% CI, 0.60-1.12; log rank P = .20). A negative overall survival trend was also observed in the PD-L1–positive and total population, but IMpassion131 was not powered for this end point and the data were immature at the time of the analysis.

Although atezolizumab is not approved for use in combination with paclitaxel in breast cancer, a different combination comprising atezolizumab and nab-paclitaxel (Abraxane) is approved for adults with metastatic TNBC whose tumors express PD-L1 per an FDA-approved test. Of note, continued approval of this latter regimen hinges on its ability to prove its benefit in additional clinical trials.

Patients who are currently receiving atezolizumab in combination with paclitaxel for other approved uses should continue on the therapy, but health care professionals should take note of any adverse events associated with the doublet and report them to the MedWatch the FDA’s medical product safety reporting program. Agency officials are evaluating the use of atezolizumab and paclitaxel in ongoing clinical trials for breast cancer and “will recommend additional changes as appropriate.”

Copper Cu 64 Dotatate Gains Indication for Somatostatin Receptor+ NETs

Copper Cu 64 dotatate (Detectnet), a positron emission tomography (PET) diagnostic agent, can now be used to localize somatostatin receptor–positive neuroendocrine tumors (NETs). Doses of copper Cu 64 dotatate will be available through several nuclear pharmacies or through Curium Pharma, one of the agent’s developers.

The approval is based on data from 2 single-center, open-label studies that confirmed the efficacy of the diagnostic agent in this setting. The first study was a prospective analysis of 63 patients, 42 of whom had known or suspected NETs and 21 of whom were healthy volunteers.

Results showed that the percent reader 1 agreement for positive detection in 62 scans was 91% (95% CI, 75%-98%) and negative detection was 97% (95% CI, 80%-99%). For reader 2, these percentages were 91% (95% CI, 75%-98%) and 80% (95% CI, 61%-92%), respectively, for 63 scans. Lastly, the percent reader agreement for reader 3 in 63 scans was 91% (95% CI, 75%-98%) positive and 90% (95% CI, 72%-97%) negative. Similar efficacy was seen in the second study, a retrospective analysis of 112 patients, all of whom had a known history of NETs.

The approval is expected to ease shortages or delays experienced with other somatostatin analogue PET agents, according to Curium.
Devimistat Hits Target Enrollment in Phase 3 Pancreatic Cancer Trial

AVENGER 500 (NCT03504423), a pivotal phase 3 clinical trial evaluating the efficacy and safety of devimistat for patients with treatment-naive metastatic pancreatic cancer, has achieved its target enrollment of 500 patients. Enrollment will remain open for the time being, according to principal investigator Philip A. Philip, MD, who added that he hopes preliminary results will be available early next year.

“Currently, this is the only [ongoing] phase 3 trial [of a novel agent] in frontline pancreatic cancer in the world,” Philip told OncologyLive®.

“There is a lot of hope and anticipation of some good results.”

Devimistat, formerly CPI-613, is a first-in-class agent that selectively targets the mitochondrial tricarboxylic acid cycle in tumor cells, which is essential to tumor cell multiplication and survival. The agent was developed by Rafael Pharmaceuticals for use in combination with modified FOLFIRINOX in the first-line setting. The primary end points of the AVENGER 500 trial are overall response rate and progression-free survival of devimistat plus modified FOLFIRINOX versus FOLFIRINOX alone.

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

Lucitanib/Nivolumab Combo Enters Phase 2 in Gynecologic Cancers

The first patient has been enrolled in the phase 2 portion of the LIO-1 trial (NCT04042116), which will examine the combination of lucitanib plus nivolumab (Opdivo) in patients with gynecologic tumors, according to Clovis Oncology, the company developing the regimen.

Lucitanib is an investigational angiogenesis inhibitor of the tyrosine kinase activity of VEGFR 1-3, PDGFRα/β, and FGFR 1-3. The rationale to combine angiogenesis inhibitors with immunotherapy agents is based on clinical data that have suggested increased efficacy with this approach in several cancer indications.

Data from the phase 1b part of the study was presented at the 2020 European Society for Clinical Oncology Virtual Congress. The results established the recommended starting dose of lucitanib as 6 mg orally once daily in combination with nivolumab at 480 mg intravenously every 28 days.

TO READ MORE, VISIT https://bit.ly/33CdMjS

Novel Protein Is Under Exploration for Advanced Solid Tumors

Investigators are evaluating the clinical and immunological effect of the experimental, engineered fusion protein ALKS 4230 on the tumor microenvironment of several advanced, malignant solid tumors in the recently initiated phase 2 ARTISTRY-3 trial.

An intravenous dose of ALKS 4230 will be administered as lead-in monotherapy followed by ALKS 4230 in combination with pembrolizumab (Keytruda) in patients with advanced malignant solid tumors. This is the fourth trial to evaluate the investigational agent.

ALKS 4230 is a novel, engineered fusion protein composed of altered interleukin-2 (IL-2) and the high affinity IL-2 alpha receptor chain, developed to selectively multiply tumor-killing immune cells while evading the activation of immunosuppressive cells. Due to the agent’s selectivity, it is capable of enhancing the antitumor effects of existing IL-2 therapy while mitigating certain limitations with those approaches.

TO READ MORE, VISIT https://bit.ly/2Eat1qR

Bispecific Antibody Starts Phase 1 Study in Solid Tumors

CDX-527 is now under investigation in a phase 1 trial (NCT04440943) enrolling patients with advanced or metastatic solid tumors who have progressed during or following standard-of-care treatment, according to the agent’s developer, Celldex Therapeutics, Inc. CDX-527 combines the blockade of the PD-1 pathway with T-cell costimulation through CD27 into 1 molecule through the use of an IgG1-ScFv format. Preclinical data have shown stronger T-cell activation and antitumor activity with the investigational agent compared with a PD-L1 antibody in combination with a CD27 antibody.

The trial includes a dose escalation stage to establish the toxicity profile and establish the dose level for use in the expansion portion of the research. Up to 90 patients with select solid tumors will be enrolled in the expansion phase.

TO READ MORE, VISIT https://bit.ly/3c6vaQQ

Daiichi Sankyo, Gustave Roussy Form Research Partnership

A multiyear, multistudy research collaboration between Daiichi Sankyo and Gustave Roussy cancer center in Villejuif, France, will support the clinical, translational, and preclinical evaluation of 2 of the company’s lead antibody-drug conjugates: DS-1062 in advanced non–small cell lung cancer, and patritumab deruxtecan in metastatic breast cancer.

The partnership will commence with 2 Gustave Roussy-led, 2 Daiichi Sankyo-funded adaptive phase 2 trials to evaluate the safety and efficacy of the investigational agents. The adaptive study designs are expected to expedite the identification of individuals who would benefit from treatment with the antibody-drug conjugates. Characterizing markers of response and resistance will be a crux of the collaboration, Fabrice André, MD, PhD, director of research at Gustave Roussy, told OncologyLive®.

These established research initiatives will later be joined by additional studies which will explore DS-1062 and patritumab deruxtecan in combination with other agents.

TO READ MORE, VISIT https://bit.ly/3hJisc2

Ofatumumab Is Poised to Transition to CLL Patient Access Program

Patients with chronic lymphocytic leukemia (CLL) who are being treated with ofatumumab (Arzerra) will soon have to get their therapy through an oncology patient access program, as Novartis, the manufacturer, will no longer be selling the drug commercially for this indication.

The program will be facilitated through Patient Access Novartis Oncology, and a company spokesperson said they will be working with prescribing oncologists and specialty pharmacists on a transition plan. Novartis has not announced a timeline for the transition.

The patient access program will provide treatment at no cost to patients, but oncologists will have to request a prescription for their patients with CLL, which will then be made available by a dispensing pharmacy, the spokesperson told OncologyLive®. Until the access program launches, ofatumumab will continue to be made commercially available through existing prescription processes.

TO READ MORE, VISIT https://bit.ly/2EapSY5
KRAS G12C occurs in 13% of patients (1 in 8) with NSCLC, comparable to the prevalence of all EGFR mutations.\textsuperscript{1,2} Identifying these patients and learning more about the KRAS G12C mutation is a high priority.

Learn more about Finding The UNSEEN 13 at FindKRASG12C.com

EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

NSCLC Treatment Portfolio Gains RET-Targeted Therapy
by RACHEL NAROZNIAK, MA

THE PORTFOLIO OF PRECISION MEDICINE strategies for RET-mutant cancers has further expanded with pralsetinib (Gavreto), a selective kinase inhibitor that targets oncogenic RET fusions in non–small cell lung cancer (NSCLC).\(^1\)

On September 4, 2020, the FDA granted accelerated approval to pralsetinib for adults with metastatic RET fusion–positive NSCLC as detected by an FDA-approved test. The regulatory decision was based on efficacy data from the phase 1/2 ARROW trial (NCT03037385) that enrolled patients with RET-altered tumors, including metastatic RET fusion–positive NSCLC previously treated with platinum chemotherapy and treatment-naive RET fusion–positive NSCLC.\(^1\)

Results showed that pralsetinib elicited durable responses, with 57% and 70% of patients with previously treated and treatment-naïve disease experiencing a response lasting 6 months or longer, respectively. A benefit was also observed in patients with measurable central nervous system (CNS) metastases at baseline who received prior platinum chemotherapy. Responses in intracranial lesions were observed in 4 of the 8 patients with CNS metastases and included 2 CNS complete responses. Seventy-five percent of responders had a duration of response greater than or equal to 6 months.\(^2\)

In an interview with OncologyLive\(^,\) Justin F. Gainor, MD, an author of the ARROW study and director of the Center for Thoracic Cancers and of Targeted Immunotherapy in the Henri and Belinda Termeer Center for Targeted Therapies at Massachusetts General Hospital in Boston, discussed the impact the agent may have on the RET-altered NSCLC paradigm.

What was noteworthy about the efficacy data that led to the approval?
The approval was based on data from the registrational ARROW study. This was a phase 1/2 study that explored pralsetinib in RET fusion–positive lung cancer and in several other cohorts, including medullary thyroid cancer and RET fusion–positive solid tumors. In this study, the registrational data set included 87 patients with RET fusion–positive non–small cell lung cancer that had been previously treated with platinum doublet chemotherapy. Within that cohort, we observed an objective response rate of 57%. This was significantly better than what we’ve historically seen with multikinase inhibitors. Importantly, 6% of patients had a complete response. It is quite impressive for us to see complete responses in a solid tumor like lung cancer.

Within the broader cohort of patients with non–small cell lung cancer, there were 27 patients with treatment-naïve disease, and we observed an objective response rate of 70% among those patients, including 11% of patients who experienced a complete response. Collectively, these data show that use of a highly selective RET inhibitor can induce robust responses in the vast majority of patients with RET fusion–positive non–small cell lung cancer.

The central nervous system is an important sanctuary state of disease for patients with lung cancer. We’ve certainly seen in the targeted therapy field in lung cancer that it is really critical to have CNS-penetrant targeted therapies for patients with RET fusion–positive lung cancer. We know that the lifetime prevalence of brain metastases is close to 50%, so having a CNS penetrant agent is important. In the ARROW study, we saw that among patients with measurable intracranial disease at study entry, more than half of these patients had intracranial responses, suggesting that pralsetinib does enter the CNS and is capable of producing significant CNS activity.

Please describe the mechanism of action.
RET rearrangements lead to oncogenic fusion proteins that are constitutively active. We know that this activity confers a state of oncogene addiction in tumor cells, and by blocking that signal with RET tyrosine kinase inhibitors, tumor cells can undergo apoptosis. The rationale for using pralsetinib is to essentially turn off that constitutive RET signaling, leading to tumor cell kill.

Regarding safety, what adverse events (AEs) do clinicians need to be aware of when prescribing pralsetinib?
The most common AEs associated with this drug were events like fatigue, constipation, musculoskeletal pain, and increased blood pressure. The other less common AEs that we’re seeing with pralsetinib that clinicians should be aware of is that a subset of patients can experience low white blood cell counts. A subset of patients can also develop drug-induced pneumonitis, which has also been seen with other targeted therapies.

How does this approval advance the RET-altered NSCLC paradigm?
This approval is incredibly exciting. We’ve gone from having no targeted therapies for this molecular subtype of lung cancer to having 2 FDA approved therapies within several months, pralsetinib and selpercatinib [Retevmo]. Both of these agents have shown really robust systemic and intracranial activity for RET fusion–positive lung cancer. Moving forward, we need to understand the durability of these responses, as well as the underlying mechanisms of resistance to therapy. Ultimately, by understanding targeted therapy escape mechanisms, we can inform our next treatment strategies, such as possible combination regimens or next-generation RET inhibitors.

What are the next steps for pralsetinib?
Right now, pralsetinib’s approval is for RET fusion–positive lung cancer, but the ARROW study also enrolled patients with several types of thyroid cancer and other RET fusion–positive solid tumors. To date, pralsetinib has shown very robust activity in all of these malignancies. A new drug application was filed and subsequently accepted by the FDA for medullary thyroid cancer. Hopefully, down the road we will have a tumor-agnostic indication.

REFERENCES
**PIVOTAL CLINICAL TRIAL**

ARROW (NCT03037385), a phase 1/2 multicohort trial that enrolled patients with RET-altered tumors. The efficacy population comprised 87 patients with metastatic RET-fusion-positive NSCLC who progressed on platinum-based chemotherapy and 27 patients with treatment-naïve, metastatic NSCLC. RET gene fusions were identified by next-generation sequencing, fluorescence in situ hybridization, and other tests. Patients with asymptomatic central nervous system metastases, including those with stable or decreasing steroid use within 2 weeks prior to study entry, were permitted to enroll.

**BASELINE PATIENT CHARACTERISTICS**

Patients with metastatic RET-fusion-positive non–small cell lung cancer (NSCLC)

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior platinum chemotherapy (n = 87) 60 (28-85)</td>
</tr>
<tr>
<td>Treatment naïve (n = 27) 65 (30-87)</td>
</tr>
</tbody>
</table>

**Method of RET-fusion detection**

<table>
<thead>
<tr>
<th>2% 77% 45% 6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
</tr>
<tr>
<td>NGS</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

**Prior platinum chemotherapy (n = 87)**

- 33%
- 67%
- 41%
- 22%
- 4%

**Treatment naïve (n = 27)**

- 77%
- 21%
- 2%
- 26%
- 45%
- 6%

**Type of NGS sample:**

- Tumor sample
- Blood or plasma sample
- Unknown

**Most common RET-fusion partners**

<table>
<thead>
<tr>
<th>75% 17% 11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIF5B</td>
</tr>
<tr>
<td>CCDC6</td>
</tr>
</tbody>
</table>

**Efficacy Results in the Arrow Trial**

**Outcome**

<table>
<thead>
<tr>
<th>Pralsetinib</th>
<th>Patients with metastatic RET-fusion-positive NSCLC previously treated with platinum chemotherapy (n = 87)</th>
<th>Patients with treatment-naïve, metastatic RET-fusion-positive NSCLC (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR assessed by BICR (95% CI)</td>
<td>57.0% (46.0%-68.0%)</td>
<td>70.0% (50.0%-86.0%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>5.7%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Partial response</td>
<td>52.0%</td>
<td>59.0%</td>
</tr>
<tr>
<td>DOR, median months (95% CI)</td>
<td>NE (15.2-NE)</td>
<td>9.0 (6.3-NE)</td>
</tr>
<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>80.0%</td>
<td>58.0%</td>
</tr>
</tbody>
</table>

BICR, blinded independent central review; DOR, duration of response; NE, not estimable; ORR, overall response rate.

**Warnings and Precautions**

- Interstitial lung disease/pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic events
- Risk of impaired wound healing
- Embryo-fetal toxicity

**Commonly Reported Adverse Events in the Arrow Study**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pralsetinib (N = 220)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35.0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>35.0%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>32.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>23.0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20.0%</td>
</tr>
<tr>
<td>Edema</td>
<td>20.0%</td>
</tr>
</tbody>
</table>

*Only includes a grade 3 adverse event.

**Mechanism of action:**

- Pralsetinib is a kinase inhibitor of wild-type RET and oncogenic RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M, RET M918T) with half maximal inhibitory concentrations less than 0.5 nM.
- In mice implanted intracranially with tumor models expressing KIF5B-RET or CCDC6-RET, pralsetinib prolonged survival.

**How supplied:**

- 100-mg immediate release, hydroxypropyl methylcellulose hard capsule.

**Dosing:**

- 400 mg once daily on an empty stomach
  - Food should not be consumed for at least 2 hours before and at least 1 hour after taking pralsetinib.
  - Treatment can continue until disease progression or unacceptable toxicity.

**Company:** Blueprint Medicines Corporation

**FDA approval—September 4, 2020**

FDA grants accelerated approval to pralsetinib (Gavreto) for patients with metastatic RET-fusion-positive non–small cell lung cancer (NSCLC) as detected by an FDA-approved test.

**Reference**

NOW APPROVED

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

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

R/R DLBCL=relapsed/refractory diffuse large B-cell lymphoma.

➤ 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.
factor (G-CSF) administration. Withhold MONJUVI based on the severity of neutropenia for signs of infection. Consider granulocyte colony stimulating factor to treat neutropenia in 3.7% of patients.

Neutropenia led to treatment discontinuation in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and anemia in 7%. Thrombocytopenia led to treatment discontinuation in 25% of patients, thrombocytopenia in 6%.

Infusion-Related Reactions

MONJUVI can cause infusion-related reactions (IRRs). In L-MIND, infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These infusion-related reactions occurred in 2.5% of the 81 patients. Infusion-related reactions led to treatment discontinuation in 15% due to an adverse reaction occurred in 15% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%.

Infections

Infections were respiratory tract infection (24%), urinary tract infection (17%), and decreased appetite. Infections were reported in 2.5% of the 81 patients. 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 1.2%.

SAFETY PROFILE

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

Serious adverse reactions occurred in 52% of patients who received MONJUVI.

- Serious adverse reactions in ≥8% 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%), infections (27%) and anemia (7%)

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

MONJUVI® (tafasitamab-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 (ASCT).

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

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
MONJUVI can cause infusion-related reactions. In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypotension. 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 pregnancy 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 a 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 |
|-------------------------------------------------|------------------|------------------|
| Adverse Reaction                                | All Grades (%)   | Grade 3 or 4 (%) |
| Blood and lymphatic system disorders            |                  |                  |
| Neutropenia                                     | 51               | 49               |
| Anemia                                          | 36               | 7                |
| Thrombocytopenia                                | 31               | 17               |
| Febrile neutropenia                             | 12               | 12               |
| General disorders and administration site conditions |               |                  |
| Fatigue*                                       | 38               | 3.7              |
| Pyrexia                                         | 24               | 1.2              |
| Peripheral edema                                | 24               | 0                |
| Gastrointestinal disorders                      |                  |                  |
| Diarrhea                                        | 36               | 1.2              |
| Constipation                                    | 17               | 0                |
| Nausea                                          | 15               | 0                |
| Vomiting                                        | 15               | 0                |
| Respiratory, thoracic and mediastinal disorders |                  |                  |
| Cough                                           | 26               | 1.2              |
| Dyspnea                                         | 12               | 1.2              |
| Infections                                      |                  |                  |
| Respiratory tract infection†                    | 24               | 4.9              |
| Urinary tract infection†                        | 17               | 4.9              |
| Bronchitis                                      | 16               | 1.2              |
| Metabolism and nutrition disorders              |                  |                  |
| Decreased appetite                              | 22               | 0                |
| Hypokalemia                                     | 19               | 6                |
| Musculoskeletal and connective tissue disorders |                  |                  |
| Back pain                                       | 19               | 2.5              |
| Muscle spasms                                   | 15               | 0                |

* 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%), dysesthesia (6%)
- Respiratory, thoracic and mediastinal disorders: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- Skin and subcutaneous tissue disorders: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)
MONJUVI® (tafasitamab-cxix)

Table 4 summarizes the laboratory abnormalities in L-MIND.

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

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

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

**Immunogenicity**

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

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

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

**Clinical Considerations**

Fetal/Neonatal Adverse Reactions

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

**Data**

**Animal Data**

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

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

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

**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.

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COVID-19 in the Clinic

*Covid-19 in the Clinic*

OncologyLive® traces the impact of COVID-19 from bedside to bench.

COVID-19 Shines Light on Disparities in Care for Patients With Cancer

*by Audrey Sternberg*

**Findings Have Shown That** patients with cancer are at an increased risk of developing severe illness due to coronavirus disease 2019 (COVID-19). The COVID-19–positive cancer population is also more likely to be African American, present at an older age, and have an increased risk of intensive care stay and intubation, as well as a longer duration of hospital and intensive care time, compared with the COVID-19–positive population without cancer.1

As more data become available, patterns of health inequities during the COVID-19 pandemic emerge. During presentations delivered as part of the COVID-19 and Cancer meeting, hosted by the American Association for Cancer Research, investigators highlighted biologic and socioeconomic factors that play a role in the growing disparities in care and severity of risk of complications for patients with cancer and COVID-19.2

The United States has the highest number of reported COVID-19 cases in the world, with deaths occurring more often in patients with advanced age and comorbidities. The disparity for COVID-19 deaths is seen for all age groups, with African Americans showing the highest death rates at any age. Compared with non-Hispanic Whites, both African American and Hispanic COVID-19 deaths outpace those of non-Hispanic Whites, even at younger ages.3

“In my own state of Michigan, African Americans’ share of cases, as well as deaths, greatly outstrip the proportion of African Americans in the state population,” John M. Carethers, MD, professor and chair of the Department of Internal Medicine and professor of human genetics at the University of Michigan Medical School in Ann Arbor, said during his presentation.2 “Overall, African Americans make up 13% of the population but make up 23% of COVID-19 deaths. If you assess this per 100,000 population, [deaths in] non-Hispanic Whites occur at a rate of 27 per 100,000, [whereas] African Americans are at a whopping 62 per 100,000.”

In a cross-sectional study evaluating the association between COVID-19 infection and mortality rate from 369 counties of 7 states, African Americans were observed to be more vulnerable to the virus than any other ethnic group. Variables irrespective of race that were most closely associated with death rates in the study were medical disabilities, lack of grocery mobility, and poverty.3

In a cohort of patients hospitalized with laboratory-confirmed COVID-19, cancer status, race and ethnicity, and descriptive statistics for baseline characteristics were collected to analyze the cumulative effects in patient mortality. Findings showed a trend toward higher rates of death in African Americans, men, and patients on Medicare/Medicaid in the COVID-19–positive cancer population, but those associations were not found to be statistically significant.1

“There was a disproportionate number of men and specifically, African American men, who were coming in and requiring hospitalization,” Steven S. Chang, MD, director of the Head and Neck Cancer Program at the Henry Ford Cancer Institute in Detroit, Michigan, said while presenting the data. “Once they are in the hospital, their outcomes were similar regardless of race, but the factors that led to the emergency room door were probably the drivers of morbidity.”

**Can Baseline Biological Factors Explain COVID-19 Outcomes?**

It has been surmised that higher mortality and infection rates among racial minorities may be due to disproportionally increased non-COVID-19 comorbidities seen in stratified patient subgroups.

“African Americans in particular carry more health conditions making them more susceptible to COVID-19, with a higher
vulnerability index in the middle and older ages and higher numbers of comorbid risk factors...compared with non-Hispanic Whites,” Carethers said.

However, recent studies suggest that this may not represent the full scope of the issue. In one study, the risk of testing positive for the virus by race and ethnicity compared with the non-Hispanic White population carried higher odds ratios (ORs) in patients who identified as Hispanic/Latino (age-adjusted OR, 2.69; 95% CI, 2.14-3.39), African American (age-adjusted OR, 3.69; 95% CI, 2.83-4.81), and Asian (age-adjusted OR, 1.87; 95% CI, 1.36-2.58). When adjusted for sex, history of diabetes, heart disease, lung disease, kidney disease, current smoker status, and body mass index, corresponding ORs in the same patient subgroups did not change drastically: multivariate OR, Hispanic/Latino (2.68; 95% CI, 2.13-3.38); African American (3.51; 95% CI, 2.68-4.60); and Asian (1.97; 95% CI, 1.43-2.73).4

Hydroxychloroquine, a drug used to prevent and treat COVID-19 in the early days of the pandemic, was since found to offer no benefit to infected patients.5 In patients who have a sodium channel variant known as p.Ser1103Tyr-SCN5A, seen among 1 in 13 African Americans, there is a higher risk of heart arrhythmia and sudden cardiac death, which can be exacerbated by COVID-19-related conditions such as hypoxia, myocardial injury, cytokine storm, and use of QTc-prolonging drugs.6

“The coalescing of these 3 items puts the patient at extremely high risk for sudden cardiac death,” said Carethers, although he noted that there aren’t any study findings to confirm this association.

Sexual dimorphic responses to COVID-19 may be due to expression of the receptor ACE2 and serine protease TMPRSS2 for S protein priming, which both are necessary cellular factors for virus entry to human cells.7 Preexisting conditions may explain why these have upregulated expression in certain patients. In patients with asthma, those who were men, African American, and/or had diabetes all had increased ACE2 and/or TMPRSS2 from collected sputum cells, providing rationale for monitoring these subgroups for COVID-19 outcomes.8 Patients with lung diseases, including cancer, also have increased expression of TMPRSS2.9

**IMPACT OF SOCIO-ECONOMIC FACTORS**

Carethers also pointed out that a societal picture could provide the greatest rationale for disparities in infection rates and outcomes in patients with COVID-19.

“It starts with socioeconomic inequality, where you have lower status, lower level of education, and difficult access to health care that causes downstream consequences,” Carethers said.2,10 “This in turn causes changes to physiology, which include alterations to the lung and gut microbiome, increased localized inflammation, and compromised immunity. That affects the pathophysiologic health morbidities of cancer, obesity, diabetes, COPD [chronic obstructive pulmonary disorder] and asthma, hypertension, and cardiovascular and chronic kidney disease.”

The high unemployment rate, in large part caused by the pandemic, worsens inequities in health care. According to the Bureau of Labor and Statistics, the rate of unemployment in May was at 13.3%, the highest since level since the Great Depression. Importantly, job loss for many patients also leads to loss of medical insurance and in turn reduces access to cancer screening.

In a study that used data from the National Health Interview Survey, the relationship between unemployment, health insurance status, and cancer screening was examined to inform the potential lasting effects of COVID-19. Forty percent of patients who were unemployed were also uninsured versus roughly 10% of those who were currently working, with unemployed individuals more likely to have Medicaid. Racial minority groups were also more likely to be unemployed than employed, including Hispanic and African American respondents.11

Controlling for nonmodifiable risk factors, unemployed individuals were less likely to be up to date on breast and colorectal cancer screenings, leading the investigators to conclude that unemployment is adversely associated with guideline-recommended care.

“This is concerning because we know that cancer screening can potentially save lives,” Stacey A. Fedewa, PhD, an epidemiologist and senior principal scientist in the Surveillance and Health Services Research Program at the American Cancer Society, said while presenting the study data. “Because a growing number of people are losing their jobs and several racial and ethnic minority groups are more likely to be unemployed, this could drive disparities even further than what is seen now.”

Carethers concluded by reflecting on how socioeconomic and biological factors together explain why these differences in outcome may exist. “In many ways, the disparities observed with COVID-19 may start from socioeconomic vulnerabilities that enter a vicious cycle of comorbidities, increased ACE2 and TMPRSS2 expression that [boosts] one’s susceptibility to COVID-19, and lead to severe illness and death,” he said. “If one survives, they become more vulnerable from the aftereffects of COVID-19 and more socioeconomic disadvantaged with loss of jobs.”

Although Carethers acknowledged that there is no quick fix for these issues, he is optimistic that bringing these data to the surface will help undermine some of the structural issues that are responsible for aggravating health disparities. “COVID-19 has enhanced the visibility of some of the [structural inequalities] that we have in the United States, and most people are seeing that,” he said.
Emotional AEs Remain a Blindspot in Oncology Care

by RACHEL NAROZNIAK, MA

PATIENTS WITH CANCER CONTINUE to find their health care providers “more helpful” in managing physical adverse effects (AEs) resulting from cancer therapy compared with emotional or mental health AEs, according to new data in the 2020 State of Cancer Survivorship Survey from the National Coalition for Cancer Survivorship (NCCS).[1]

Findings from the latest evaluation build on the 2018-2019 State of Cancer Survivorship Survey, which fielded responses from 1380 patients with cancer who completed treatment or were receiving therapy for an initial diagnosis or disease recurrence, had metastatic cancer, or were being treated with immunotherapy. Responses from the earlier survey indicated that providers were more helpful in addressing nausea and vomiting, for instance, but “less helpful” in managing mental health–related AEs such as fatigue, anxiety, and depression.[2] Although patient ratings of provider helpfulness with mental health AEs increased from 2018-2019 to 2020, this nevertheless remained the prevailing sentiment in the 2020 analysis.[1]

In contrast with the 2018-2019 survey, which presented data on whether patients felt their providers were “very helpful” or “somewhat helpful,” the 2020 survey specifically focused on the AEs for which patients said their provider was “very helpful.” Less than half of the 840 patients with cancer and survivors who participated nationwide between April 15 and May 1, 2020, said their provider was helpful in addressing specific AEs, many of which were emotional in nature (TABLE1). Although 49% of participants reported feeling overly tired, just 35% said their provider was “very helpful” in managing fatigue. Feeling overly tired was the most frequently experienced mental health AE among patients (49%), followed by depression and/or anxiety, which affected 30%. Thirty-four percent of respondents classified their provider as very helpful in managing this AE.[1] “Fatigue, anxiety, and depression are some of patients’ key concerns and are also the concerns that patients feel like they’re getting the least help with. This was definitely consistent between the 2 surveys. To me, the biggest takeaway [from the report] is that we’ve done a pretty good job of dealing with most of the physical issues, but more work is to be done when it comes to managing the emotional issues,” Shelley Fuld Nasso, MPP, who is CEO of NCCS, said in an interview with OncologyLive®.

The third most prevalent mental health AE in the 2020 analysis was uncertainty about the cancer status, which affected 24% of patients. The top 3 physical AEs were loss of appetite/taste (28%), muscle/joint pain (27%), and nausea/vomiting or diarrhea (27%).

The 2020 survey included patients and survivors who had received a diagnosis of cancer within the past 2 years. Participants presented with a variety of malignancies at different stages. NCCS set subgroup quotas to ensure that the national sample was representative of the cancer population in the United States regarding age, gender, race/ethnicity, and region.[1]

In the 2018-2019 assessment, feeling overly tired, anxiety, and depression were also the 3 most common mental health AEs, affecting 67%, 58%, and 44% of participants during and after treatment, respectively. Forty-one percent of patients who experienced fatigue still felt overly tired at the time of the survey, treatment-related anxiety endured in 40%, and 28% percent of patients had ongoing depression. Regarding patient satisfaction with the care received, 24% of patients reported that their provider was very helpful in addressing feeling overly tired, whereas 39% indicated that the provider was “somewhat helpful.” Of note, feeling overly tired was one of the most severe AEs experienced across all participating patient subgroups, such as patients with metastatic disease and those receiving immunotherapy.[2]

The percentages of 2018-2019 respondents who perceived their provider as very helpful and somewhat helpful in mitigating anxiety were similar to this year’s, at 25% and 40%, respectively. Twenty-four percent of patients called the care they received for their depression very helpful, whereas 41% said it was somewhat helpful.

Although fatigue and mental health issues are the most prevalent AEs reported by patients and survivors alike, the 2020 survey data affirm what was apparent in the 2018-2019 responses: Patients feel they are not receiving adequate care for these pervasive emotional AEs. This sentiment is illustrated...
in the fact that less than one-third of patients discuss fatigue and anxiety/depression with their provider. Specifically, just 28% and 29%, respectively, of 638 patients from the national sample indicated that these elements of functional status were addressed in a conversation with their provider.1

The 2020 responses at large “show that we continue to focus on the physical aspects of cancer and cancer treatment and not as much on all the other ways that cancer [affect] someone’s life, and that’s where people really need support,” Shelley said.

RESPONSES REVEAL GREATER SATISFACTION OVER PHYSICAL AEs

In both the 2020 and 2018-2019 State of Cancer Survivorship Surveys, patient perception of provider helpfulness was markedly higher in reviews of physical versus emotional AE management. For example, 54% of 2020 survey respondents reported that their provider was very helpful in addressing nausea/vomiting or diarrhea, which affected 27% of patients and was the fifth most common AE of any kind. In addition, 54% of participants stated that their health care team was very helpful in instances of skin irritation and other dermatologic problems, the 10th most frequent AE observed in this group of patients. 1

Patient satisfaction with their care for physical concerns was similarly high in the 2018-2019 survey, with 51% of participants identifying their health care team as very helpful in instances of nausea/vomiting or diarrhea. Forty-one percent of patients classified their provider as very helpful with dermatologic problems.2 Notably, 61% of patients receiving immunotherapy (n = 262) said providers were very helpful in addressing dermatologic problems. The top 3 physical AEs to affect patients during/after therapy in the 2018-2019 survey were nausea/vomiting or diarrhea (49%), muscle/joint pain (45%), and neuropathy (38%).

Overall, excluding memory loss/cognitive issues, most respondents of the earlier survey said their care team was somewhat helpful at addressing their symptoms, with far fewer indicating that the physician attention was very helpful. However, the AEs assessed by this portion of the 2018-2019 survey were mainly physical: muscle/joint pain; fever/chills; and bone, joint, and soft tissue issues, among 8 other physical complaints. In contrast, just 4 mental health AEs—anxiety, depression, feeling overly tired, and memory loss/cognitive issues—were evaluated.

The persisting trends relative to patient satisfaction—contentment with management of their physical AEs and discontent with the oversight of emotional and mental health toxicities—are likely due in part to the large volume of patients seen in an oncology practice. “These practices have a huge number of patients, and the amount of time [clinicians] have for patients is limited,” Shelley said.

These patterns can also be attributed to payment models’ focus on reducing hospitalizations and emergency department visits. For example, the Centers for Medicare & Medicaid Services’ Oncology Care Model rewarded participating practices that cut hospitalization and emergency department visits.3

“I think that’s why care teams have done a good job of triaging the kinds of [AEs] that might cause a patient to end up in the emergency department or hospital, and that’s important for patients, but then you have to go a little bit deeper into the other issues that cause quality-of-life or functional status issues for patients. These problems might not necessarily land patients in the ER but do affect their ability to [achieve] a strong quality-of-life and functional status,” Shelley said.

### Fast Facts

**2020 NCCS Survey**

**Key Takeaways**

- “Doctor Knows Best” about treatment is the prevailing mindset of patients with cancer nationally (61%), and majorities say they are satisfied with their care (50%).
- However, patients who report being more involved in treatment decisions tend to have more positive posttreatment experiences (59%).

**Mindset**

- “Doctor Knows Best” about treatment is the prevailing mindset of patients with cancer nationally (61%), and majorities say they are satisfied with their care (50%).
- However, patients who report being more involved in treatment decisions tend to have more positive posttreatment experiences (59%).

**Expectations**

- Patients who are “connected” to an advocacy group have higher expectations of care and their health care providers (HCPs).
- These patients tend to be interested in a range of resources to help them with decision-making and self-advocacy.

**Adverse effects (AEs)**

- Fatigue and mental health issues, such as depression and anxiety, continue to be the most common AEs (TABLE).
- Patients feel that HCPs are not helpful when addressing these AEs post treatment (65% and 66%, respectively).

**Survivorship concerns**

- A majority of patients discussed posttreatment expectations (n = 531; 62%); however, few received additional information.
- Exercise and nutrition (34%), emotional or psychological support (24%), and financial services/support (10%) were among the least-discussed posttreatment topics.

**Demographic differences**

- Key audiences had greater posttreatment concerns: Patients treated with chemotherapy, younger patients, Black and Hispanic populations, and women.

**TABLE. SHARED AEs FOR WHICH NCCS SURVEY PARTICIPANTS CALLED HCPs “VERY HELPFUL”**

<table>
<thead>
<tr>
<th>AE</th>
<th>2018-2019 (n = 1380)</th>
<th>2020 (n = 840)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting or diarrhea</td>
<td>51%</td>
<td>54%</td>
</tr>
<tr>
<td>High or low blood pressure</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>Skin irritation, dermatologic problems</td>
<td>41%</td>
<td>54%</td>
</tr>
<tr>
<td>Muscle/joint pain</td>
<td>28%</td>
<td>39%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>27%</td>
<td>35%</td>
</tr>
<tr>
<td>Feeling overly tired</td>
<td>24%</td>
<td>35%</td>
</tr>
<tr>
<td>Depression</td>
<td>24%; 25%</td>
<td>34%</td>
</tr>
<tr>
<td>Memory loss/cognitive issues</td>
<td>14%</td>
<td>23%</td>
</tr>
</tbody>
</table>

**Presentation to Patient**

- Physical AE
- Mental health AE

AE, adverse effect; HCP, health care provider; NCCS, National Coalition for Cancer Survivorship.

*In the 2020 survey, depression and anxiety were evaluated as 1 AE. In the 2018-2019 analysis, they were evaluated separately and demonstrated the following values: depression, 24%; anxiety, 25%.*
Survivorship

to Shelley: “[Some patients] are just not being asked about these adverse events and are not as willing to bring them up on their own; therefore, they’re not being directed to resources to help them.”

Among the national sample of patients with cancer/survivors in the 2020 survey, “doctor knows best” was the default mentality. Respondents were more likely to rely on their doctor to select the best treatment option than to be involved in the research and decision-making process by almost a 3:1 margin (61% vs 22%), whereas 18% of patients were “somewhere in the middle.” Data from the national sample additionally showed that patients’ active participation in treatment selection translated to a higher sense of posttreatment preparation and a greater likelihood that patients would perceive the posttherapy medical care received as “excellent” compared with those who relied on their doctor (35% vs 50% and 59% vs 50%, respectively). However, just 53% of patients took advantage of any resource that their health care team offered to aid the treatment experience.1

Decision-making behavior differed between the national sample and patients who opted in to communication with NCCS (n = 479). Responses from this subgroup indicated that 35% of patients depended on their doctor, 35% took an active role, and 30% remained somewhere in the middle.

These data led NCCS to surmise that patients affiliated with an advocacy group such as NCCS have higher expectations of their providers and care and are more likely to seek out resources that can aid decision-making and self-advocacy. For example, 25% of NCCS-connected patients saw a psychologist or psychiatrist versus 8% of the national sample. This subpopulation was also more likely to obtain a posttreatment survivorship plan compared with nonaffiliated respondents (28% vs 17%).

The findings from the 2020 comparison of NCCS-connected patients and the national sample attest to the value of patient advocacy groups, Shelley said. Further, by stratifying the individuals who self-advocate and those who are reluctant to become involved, choosing instead to rely on their provider, the report also affirms that work must be done to improve the patient/survivor experience and must include patient-physician conversations about specific, often unaddressed AEs. “We need to build a system that provides the right resources for patients, even if they are not going to be the ones who research all the available treatments or how to address an adverse event or long-term effect that no one told them about,” Shelley said. “We and other patient advocacy groups educate patients and try to empower them to be their best advocate, and that’s incredibly important, but we have to also focus on the system, as well, to ensure that it still works for the people who can’t self-advocate.”

REFERENCES

OncLive® Honors 15 Cancer Care Pioneers

2020 Winners Reflect International Nature of Oncology Practice

by JASON HARRIS

THE 2020 CLASS OF Giants of Cancer Care® award winners hail from around the globe, coming from locales such as Lagos, Nigeria; Amsterdam, the Netherlands; Brussels, Belgium; and Philadelphia, Pennsylvania. But no matter where their journeys began, each is now a world-renowned leader in oncology practice.

The honorees can take credit for changing practice for the better and improving patient care across a range of malignancies. Their peers have recognized them as people who are not just exceptional doctors, but also innovators in their respective fields.

This year’s class marks the eighth consecutive year that OncLive® has saluted the physician-scientists who are shaping oncology practice, bringing the total number of honorees recognized through the Giants of Cancer Care® program to 113. The 2020 award winners and their respective categories are:

- Martine J. Piccart, MD, PhD—Breast Cancer
- Laura J. van’t Veer, PhD—Cancer Diagnostics
- Clifford A. Hudis, MD—Community Outreach/Cancer Policy
- Hope S. Rugo, MD, FASCO—Education
- Margaret A. Tempero, MD—Gastrointestinal Cancer
- Olufunmilayo Falusi Olopade, MD—Genetics/Prevention
- Dean F. Bajorin, MD—Genitourinary Cancer
- Robert L. Coleman, MD—Gynecologic Malignancies
- Susan M. O’Brien, MD—Leukemia
- Tony S. K. Mok, MD—Lung Cancer
- George P. Canellos, MD—Lymphoma
- Keith T. Flaherty, MD—Melanoma & Other Skin Cancers
- Sagar Lonial, MD—Myeloma
- Richard J. Gralla, MD—Supportive, Palliative, and/or Geriatric Care
- Maura L. Gillison, MD, PhD—Translational Science

This year’s Giants will accept their awards during a video presentation that will air Thursday, November 5 at 7:30 pm EST during the 38th Annual CFS® conference, hosted by Physicians’ Education Resource®, LLC (PER®).

Dr Hudis, a breast cancer specialist who now serves as CEO of the American Society of Clinical Oncology, put the exploratory nature of oncology practice into perspective during an interview with OncLive® in advance of the ceremony. He is scheduled to deliver the Giants of Cancer Care® Lecture at CFS®.

“To be an oncologist is to be a researcher,” said Hudis, who started his medical career in Philadelphia. “Fundamentally, this is a new field. We don’t have optimal therapies for so many of the diseases that we treat. What that means is that the challenge ahead of us is to raise the bar—to do research.”

This year’s Giants have touched the lives, and saved the lives, of hundreds of thousands of patients worldwide. Olopade applied the lessons she learned treating patients on the South Side of Chicago, Illinois, to women in West Africa. van’t Veer began her career at The Netherlands Cancer Institute, where she helped launch the Netherlands Collaborative Group on Hereditary Breast Cancer. Mok’s research helped to establish the importance of the EGFR mutation in East Asian patients with non–small cell lung cancer.

This year’s award recipients were chosen from a field of more than 800 clinicians and investigators, a record number of nominees that represents a 32% increase over 2019. A 7-member steering committee winnowed the nominees down to 75 finalists, all of whom would have been worthy recipients. An elite selection committee of more than 120 hematologists and oncologists then voted to choose the winners. The Giants of Cancer Care® award is particularly meaningful because the winners know their efforts have generated interest and respect from other cancer care professionals around the world.

OncLive® began the Giants of Cancer Care® program in 2013 to honor clinicians and investigators who have contributed to advancements in the understanding of cancer and the treatment of patients. Recipients must possess selflessness, compassion for patients, and a desire to understand and develop life-changing anticancer treatments.

“I am deeply moved by this nomination,” said Dr Piccart, a professor of oncology at the Université Libre de Bruxelles and director of the Medicine Department at Jules Bordet Institute in Brussels, Belgium. “I think it means that my peers, my colleagues, value my research efforts over the past 20 years.”

Mike Hennessy Jr, president and CEO of MJH Life Sciences®, parent company of OncLive®, called the Giants “oncology legends” and praised honorees for their tireless efforts on behalf of patients and their families.

“To the eighth year of issuing the Giants of Cancer Care® awards, the program has grown bigger and better than we ever expected,” Hennessy said. “This year’s winners represent a group of remarkably talented scientists and physicians. The impact they’ve had on cancer research and treatment is truly beyond measure, and we are honored to call them Giants of Cancer Care®.”
2020 RECIPIENTS

BREAST CANCER
Martine J. Piccart, MD, PhD
Université Libre de Bruxelles/Jules Bordet Institute

• Dr Piccart is a professor of oncology at the Université Libre de Bruxelles and director of medicine at the Jules Bordet Institute in Brussels, Belgium.
• She is the principal or coprincipal investigator for several major clinical trials, including HERA, MINDACT, and ALTTO. She is currently leading AURORA, a trial evaluating precise molecular analyses of primary and metastatic breast cancer tumor samples to better understand the evolution of metastasis and the mechanisms of drug resistance.
• A leader in research collaboration, Dr Piccart is cofounder and chair of the Breast International Group (BIG), which unites over 55 academic research groups. BIG is conducting over 25 clinical trials and developing numerous research programs. Dr Piccart also helped to establish the translational cancer research-based organization TRANSBIG.
• Dr Piccart has won the Léopold Griffuel Award for Translational and Clinical Research from the French ARC Foundation for Cancer Research (2018), the KNAW Bob Pinedo Award (2018), the William L. McGuire Award and Lectureship (2009), the St Gallen International Breast Cancer Award (2017), the Umberto Veronesi Award for the Future Fight Against Cancer (2012), the David A. Karnofsky Memorial Award (2013), and the Breast Cancer Research Foundation Jill Rose Award for outstanding research excellence (2009).

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

• Dr van ’t Veer is credited with inventing MammaPrint, a genomic test for women with estrogen receptor–positive, HER2-negative, early-stage breast cancer that analyzes the activity of 70 genes to determine a patient’s 10-year risk for recurrence and/or metastasis.
• She chairs the biomolecular committee of the I-SPY 2 trial and is serving as principal investigator of the Athena Breast Health Network at UCSF, a 150,000-women cohort study evaluating new paradigms to enhance breast health. She also is a principal investigator for the National Institutes of Health Big Data to Knowledge Center on Genomics, facilitating worldwide standardization for sharing annotated genomics data.
• At UCSF, Dr van ’t Veer serves as a professor of laboratory medicine and as director of applied genomics at Helen Diller Family Comprehensive Cancer Center. She also holds the Angela and Shu Kai Chan Endowed Chair in Cancer Research.
• During her career, she has won the European Cancer Organisation Clinical Research Award (2017), the European Inventor Award (2015), the inaugural Harry and Edith Gladstein Award from the Indiana University School of Medicine (2009), the European Society for Medical Oncology Lifetime Achievement Award for Translational Research in Breast Cancer (2007), the Van der Schueren Award and Lecture for European Breast Cancer Research (2006), and the International Agency for Research on Cancer Medal of Honor (2005).

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

• Dr Hudis has served as ASCO CEO since 2016. He is also executive vice chair of the ASCO Conquer Cancer Foundation and chair of the Board of Governors for ASCO’s CancerLinQ data analytics initiative. Before joining ASCO full time, he served as president during the organization’s 50th anniversary year (2013-2014).
• Under his leadership, ASCO has developed initiatives involving new educational offerings, scientific research, and emerging technologies that are helping to shape evidence-based health policy.
• From 1998 to 2016, Dr Hudis served as chief of the Breast Medicine Service at Memorial Sloan Kettering Cancer Center, where he led studies that integrated hematopoietic growth factors, taxanes, and targeted agents into the breast cancer treatment paradigm.
• He specifically helped translate the model developed by Larry Norton, MD, a 2016 Giants of Cancer Care® award winner, and Richard Simon, DSc, into dose-dense chemotherapy as an adjuvant therapy, which became the standard of care for patients with curable breast cancer.
• During his career, Dr Hudis has received a Lifetime Achievement Award from his alma mater, Drexel University (2018), and the Pennsylvania Breast Cancer Coalition Vivian and Meyer P. Potamkin Foundation Prize (2017). He was also named to the Winship 80 list of influential oncology leaders in celebration of the founding of the Winship Cancer Institute at Emory University in Atlanta, Georgia.
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2020 RECIPIENTS

EDUCATION
Hope S. Rugo, MD, FASCO
University of California San Francisco (UCSF)/Helen Diller Family Comprehensive Cancer Center

• Dr Rugo has advanced breast cancer care through her work as a clinical research leader and as a noted lecturer at conferences throughout the world. At UCSF, she leads the Breast Forum, a discussion platform for patients, families, and caregivers.
• As an investigator, Dr Rugo was instrumental in the EMBRACA and ABRAZO studies into the efficacy of talazoparib (Talzenna), a PARP inhibitor that the FDA approved in 2018 for patients with HER2-negative locally advanced or metastatic breast with germline BRCA mutations.
• She was a key investigator in the IMpassion130 trial, which led to the FDA approval of alezolizumab (Tecentriq) in combination with nab-paclitaxel (Abraxane) in triple-negative breast cancer. She leads the ongoing TROPICS-02 trial into sacituzumab govetecan and has played crucial roles in dozens of clinical trials including ASCENT, KEYNOTE 355, I-SPY 2, PALOMA 2, and SOLAR1.
• Dr Rugo’s work has resulted in regulatory approvals for scalp-cooling technology to reduce chemotherapy-induced alopecia and a steroid mouthwash to relieve stomatitis from targeted therapy.
• Dr Rugo is director of Breast Oncology and Clinical Trials Education and a professor of medicine at Helen Diller, and co-chair of the Translational Breast Cancer Research Consortium Triple Negative Working Group.
• She has been honored by the Friends of the Breast Care Center (2006) and the CancerCare National Organization (2010), and won a PRIMO Women in Oncology Award in 2019.

GASTROINTESTINAL CANCER
Margaret A. Tempero, MD
University of California, San Francisco (UCSF)/Helen Diller Family Comprehensive Cancer Center

• Dr Tempero is a pioneering investigator into novel treatments for pancreatic ductal adenocarcinoma, particularly in the use of antibody-based therapies and the fixed-dose rate concept for gemcitabine.
• Her research helped establish the rationale for using serum carbohydrate antigen 19-9 as a surrogate marker for survival in clinical trials. Her group currently is working on assessing molecular subtypes in pancreatic cancer.
• While on the faculty at the University of Nebraska in the 1990s, Dr Tempero directed the first Gastrointestinal Cancer SPORE dedicated to pancreatic cancer. She organized the first pancreas cancer think tank in 1999 and helped lead the National Cancer Institute’s Pancreatic Cancer Progress Review Group in 2000. She also has chaired the National Comprehensive Cancer Network Guidelines Panel on Pancreatic Cancer since 2000.
• Throughout her career, Dr Tempero has held a variety of academic and professional leadership posts. She is the current director of the UCSF Pancreas Center and the Rombauer Family Distinguished Professor in Pancreas Cancer Clinical and Translational Science at the Helen Diller Family Comprehensive Cancer Center. Previously, she was the center’s founding deputy director and UCSF’s chief of the Division of Medical Oncology.
• Dr Tempero served as president of American Society of Clinical Oncology (2004) and as a member of the FDA’s Oncologic Drug Advisory Committee (2007-2011).

GENETICS/PREVENTION
Olufunmilayo Falusi Olopade, MD
University of Chicago

• Dr Olopade is an expert in cancer risk assessment whose research findings have elucidated molecular diversity in patients with breast cancer. She demonstrated that women of African descent are significantly more likely to have estrogen receptor-negative breast cancer, which develops at a younger age. Her findings also showed that this patient population requires testing and genetic screening at a younger age and more often than white women.
• In 2005, the John D. and Catherine T. MacArthur Foundation awarded Dr Olopade with a “genius grant” for her work on translating findings on the molecular genetics of breast cancer in African and African American women into innovative clinical practices.
• She has also won the Mendel Medal (2017), American Society of Clinical Oncology Humanitarian Award (2017), Access Community Health Network’s Heroes in Healthcare Award (2005), the Phenomenal Woman Award (2003), the Doris Duke Distinguished Clinical Scientist Award (2000), and the James S. McDonnell Foundation Scholar Award (1992).
• Dr Olopade is the director of the Center for Clinical Cancer Genetics and Global Health, the Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, and associate dean for Global Health at the University of Chicago. She is also the founder of the Comprehensive Cancer Risk and Prevention Clinic at the University of Chicago and has served as the clinic’s director for nearly 30 years.
2020 RECIPIENTS

GENITOURINARY CANCER
Dean F. Bajorin, MD
Memorial Sloan Kettering Cancer Center (MSK)

- Dr Bajorin leads a long-standing research program at MSK aimed at the development of new treatment approaches for bladder and testicular cancers.
- His work in testicular cancer has been focused on reducing the adverse effects of chemotherapy and on exploring biological characteristics of tumors. In urothelial carcinoma, Dr Bajorin was a key investigator into the use of pembrolizumab (Keytruda) in the pivotal KEYNOTE-045 and KEYNOTE-052 trials. The findings led to first- and second-line indications in the malignancy.
- A medical oncologist, Dr Bajorin holds the Frederick R. Adler Senior Faculty Chair at MSK and serves as a professor of medicine at Weill Cornell Medical College. He is also the coprincipal investigator for MSK’s Bladder Cancer SPORE.
- Since 1994, Dr Bajorin has served as director of the Medical Oncology/Hematology Fellowship Training Program. Starting in 1999, he has overseen the clinical research curriculum program for training investigators.
- Dr Bajorin formerly cochaired the National Cancer Institute’s Bladder Cancer Task Force and has twice served as chair of the Genitourinary Scientific Committee for the American Society of Clinical Oncology (ASCO).
- In 2011, Dr Bajorin received ASCO’s Statesman Award, which recognizes members for extraordinary volunteer service, dedication, and commitment.

GYNECOLOGIC MALIGNANCIES
Robert L. Coleman, MD
The US Oncology Network

- Dr Coleman has been a leader in clinical research, particularly in the field of gynecologic oncology, for the past 25 years. He has published extensively, authoring more than 600 articles and book chapters on a range of topics including novel therapies and surgical strategies for ovarian cancer.
- He recently led the phase 3 ARIEL3 trial, which evaluated rucaparib (Rubraca) as maintenance therapy in patients with recurrent platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer. The FDA approved the PARP inhibitor for that patient population in April 2018 based on findings from the trial.
- Dr Coleman joined US Oncology Research as chief scientific officer in March 2020. He previously served as the Ann Rife Cox Chair in Gynecology and a professor in the Department of Gynecologic Oncology at The University of Texas MD Anderson Cancer Center (MDACC), as well as executive director of the MDACC’s Cancer Network Research Program where he developed research programs in community hospital systems. He was also a coproject leader of the MDACC Ovarian Cancer SPORE and Uterine Cancer SPORE.
- Dr Coleman won the Rosalind Franklin Excellence in Ovarian Cancer Research Award (2018). He is a past president of the Society of Gynecologic Oncology (2015) and the current president of the International Gynecologic Cancer Society. He is a codirector for GOG Partners and sits on the board of directors for the GOG Foundation.

LEUKEMIA
Susan M. O’Brien, MD
University of California, Irvine (UCI) Chao Family Comprehensive Cancer Center

- Dr O’Brien is an internationally recognized leader in the research of treatments for both chronic and acute leukemias and an expert on several important therapies that are presently used as the standard of care for chronic lymphocytic leukemia (CLL).
- Her research background includes serving as the principal investigator for more than 40 funded clinical protocols. She has authored more than 900 articles in peer-reviewed journals and numerous book chapters and abstracts. She also has served as chair of the National Comprehensive Cancer Network guidelines panel on chronic myeloid leukemia.
- Dr O’Brien led the initial clinical research into ibrutinib (Imbruvica), idelalisib (Zydelig), duvelisib (Copiktra), and acalabrutinib (Calquence) for patients with CLL and continues to investigate Bruton tyrosine kinase inhibition in CLL and other leukemias.
- In 2015, Dr O’Brien joined UCI after serving as the Ashbel Smith Professor in the Department of Leukemia, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center. At UCI, she is associate director for clinical science for the Chao Family Comprehensive Cancer Center and medical director of the Sue and Ralph Stern Center for Clinical Trials and Research. She also is a professor in the Division of Hematology/Oncology at the UC Irvine School of Medicine.
2020 RECIPIENTS

**LUNG CANCER**
Tony S. K. Mok, MD
Chinese University of Hong Kong

- Dr. Mok is a pioneering investigator in non–small cell lung cancer (NSCLC) who has helped shape the paradigm for molecularly targeted therapies and immunotherapy.
- In 2009, Dr. Mok published the results of the landmark IPASS study, which demonstrated for the first time that an EGFR inhibitor, gefitinib (Iressa), was superior to chemotherapy as a first-line treatment for patients with NSCLC, particularly those with EGFR mutations.
- In the AURA3 trial, Dr. Mok and colleagues showed that patients with NSCLC who develop a T790M resistance mutation after receiving EGFR-targeted therapy can be treated with osimertinib (Tagrisso). The New England Journal of Medicine chose the article detailing the findings as 1 of its 10 most notable articles of 2017.
- Dr. Mok also has helped define the management of ALK-positive NSCLC, notably through the PROFILE 1014 trial, which demonstrated that crizotinib (Xalkori) was superior to chemotherapy for previously untreated patients with an ALK mutation. In the immunotherapy arena, he led the KEYNOTE-042 study, establishing the PD-1 inhibitor pembrolizumab (Keytruda) as monotherapy for patients with PD-L1–positive tumors.
- Dr. Mok is the Li Shu Fan Professor of the Department of Clinical Oncology and chair of Clinical Oncology at The Chinese University of Hong Kong. He has received numerous awards, including a Lifetime Achievement Award from the European Society for Medical Oncology (2018).

**LYMPHOMA**
George P. Canellos, MD
Dana-Farber Cancer Institute (DFCI)/Harvard Medical School

- Dr. Canellos is a longtime leader in the field of lymphoma and research. He is perhaps best known for his collaborations with Vincent T. DeVita Jr, MD, the 2013 Giants of Cancer Care® award winner in this category. The pair developed the C-MOPP regimen (cyclophosphamide, vincristine, procarbazine, prednisone) for patients with non-Hodgkin lymphoma and the CVP regimen (cyclophosphamide, vincristine, prednisone) to treat indolent forms of non-Hodgkin lymphoma.
- Dr. Canellos was president of the American Society of Clinical Oncology (ASCO) from 1993 to 1994, and he also formerly served as chair of the Lymphoma Committee of the Cancer and Leukemia Group B research cooperative.
- He is a senior physician at DFCI and Brigham and Women’s Hospital. He also holds the inaugural William Rosenberg Professor of Medicine (emeritus) position at Harvard Medical School. He previously served as DFCI’s first chief of medical oncology (1975-1995).
- DFCI has named 2 awards after Dr. Canellos, and he has received many other honors during his career. These include the Karl Musshof Award from the 7th International Hodgkin Lymphoma Symposium (2007), ASCO’s Statesman Award (2007), the Ellis Island Foundation Medal of Honor (2004), and the Key to the Cure Award from the Cure for Lymphoma Foundation (1999). He was named an ASCO Oncology Luminary in 2016.

**MELANOMA**
Keith T. Flaherty, MD
Massachusetts General Hospital Cancer Center/Harvard Medical School

- A pioneer in developing molecularly targeted therapies for patients with melanoma, Dr. Flaherty led early trials into the BRAF inhibitor vemurafenib (Zelboraf) and the MEK inhibitor trametinib (Mekinist).
- Dr. Flaherty helped establish the concept of dual MAPK pathway targeting by combining BRAF and MEK inhibitors, which has improved outcomes compared with single-agent BRAF inhibitors.
- He also has been a leader in identifying mechanisms of de novo and acquired resistance to BRAF inhibitor therapy and evaluating next-generation inhibitors.
- He served as a key investigator for the phase 3 COMBI-d trial, which evaluated the BRAF inhibitor dabrafenib (Tafinlar) plus trametinib, and for the COLUMBUS trial, which tested encorafenib (Braftovi), a BRAF inhibitor, plus binimetinib (Mektovi), a MEK inhibitor. The FDA has approved both combinations in melanoma settings.
- He was the founding director of the Henri and Belinda Termeer Center for Targeted Therapies; director of clinical research at Massachusetts General Hospital; the Richard Saltonstall Endowed Chair in Oncology at Massachusetts General Hospital Cancer Center; and a professor of medicine at Harvard Medical School.
- Dr. Flaherty is immediate past president of the Society for Melanoma Research. The society honored him with a Lifetime Achievement award in 2019.
2020 RECIPIENTS

MYELOMA
Maura L. Gillison, MD, PhD
The University of Texas MD Anderson Cancer Center

- Dr Gillison has conducted seminal research in the identification and therapeutic implications of human papillomavirus (HPV) in patients with head and neck cancer. She is credited as the first investigator to establish a connection between HPV and oral cancer.
- In 2000, Dr Gillison and colleagues published findings in the Journal of the National Cancer Institute demonstrating a link between HPV-16 and oropharyngeal cancers. She was the senior investigator on a 2007 New England Journal of Medicine study showing that HPV 16 infection results in head and neck squamous cell carcinoma (HNSCC) in both men and women, and that having multiple oral sex partners increases the risk for developing these cancers. The following year, Dr Gillison and colleagues described distinct risk factor profiles for HPV16–positive and HPV16–negative HNSCCs.
- As a result of her work, the National Cancer Institute has recommended that clinical trials in HNSCC stratify tumors by HPV status.
- Dr Gillison is a professor of medicine in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center.
- She has been honored by the American Association for Cancer Research with the Richard and Hinda Rosenthal Memorial Award (2012). She was elected to membership in the National Academy of Medicine in 2016.

SUPPORTIVE, PALLIATIVE, AND/OR GERIATRIC CARE
Richard J. Gralla, MD
Albert Einstein College of Medicine/Jacobi Medical Center

- Dr Gralla has been a leading investigator into the mechanisms of chemotherapy-induced nausea and vomiting and novel therapies to help prevent and alleviate symptoms. Starting in the 1980s, his research findings have helped define the role of serotonin receptor and neurokinin-1 receptor antagonists in suppressing emesis. These include studies of ondansetron (Zofran) and aprepitant (Emend).
- He is the author of more than 200 scientific publications and in 2007, Dr Gralla and colleagues launched the peer-reviewed journal, Current Opinion in Supportive and Palliative Care.
- Active in numerous professional organizations, Dr Gralla has served on American Society of Clinical Oncology program and education committees, including as cochair of the antiemetics guidelines panel. He was president of the Multinational Association for Supportive Care in Cancer (2000-2004).
- Dr Gralla is a professor in the Department of Medicine at the Jacobi Medical Center of Albert Einstein College of Medicine and director of oncology research for the North Bronx Healthcare Network. He formerly served as the director of Ochsner Cancer Institute (1989-2000) and the director of clinical research at the Herbert Irving Comprehensive Cancer Center (2000-2002).
- He has received the Distinguished Service Award from the Multinational Association for Supportive Care in Cancer (2006) and was honored as CancerCare Physician of the Year (2005).

TRANSLATIONAL SCIENCE
Sagar Lonial, MD
Emory University/Winship Cancer Institute

- Dr Lonial, a leading authority in multiple myeloma, has been instrumental in developing monoclonal antibodies and novel combinations, and in helping to shape optimal treatment practices.
- His research helped pave the way for FDA approvals for 2 monoclonal antibodies in November 2015: daratumumab (Darzalex), which targets CD38, and elotuzumab (Empliciti), which is directed at the SLAMF7 protein.
- Dr Lonial served as a key investigator for the SIRIUS trial, which established a role for daratumumab monotherapy in heavily pretreated patients, and for the ELOQUENT-2 trial, which explored elotuzumab in combination with lenalidomide (Revlimid) plus dexamethasone in patients with progressive disease after prior therapy.
Awards await Giants honorees at last year’s ceremony.

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2019–2020
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Director, Sarcoma Center, Dana-Farber Cancer Institute
Executive Director, Clinical and Translational Research at Ludwig Institute for Cancer Research

Patrick I. Borgen, MD
Director, Maimonides Breast Center at Maimonides Cancer Center
Chair, Department of Surgery, Maimonides Medical Center

Maurie Markman, MD
President of Medicine & Science
Cancer Treatment Centers of America

Alessandra Ferrajoli, MD
Associate Medical Director and Professor, Department of Leukemia
The University of Texas MD Anderson Cancer Center

Hope S. Rugo, MD, FASCO
Professor of Medicine, Breast Oncology and Clinical Trials Education
University of California San Francisco
Helen Diller Family Comprehensive Cancer Center

Daniel J. George, MD
Professor of Medicine and Professor in Surgery, Duke University School of Medicine
Member, Duke Cancer Institute

Heather A. Wakelee, MD
Professor of Medicine (Oncology), Stanford University Medical Center
Faculty Director, Stanford Cancer Clinical Trials Office

2020 Selection Committee

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• James O. Armitage, MD
• Douglas W. Arthur, MD
• Robert C. Bast Jr, MD
• Johanna Bendell, MD
• Joseph R. Bertino, MD
• Michael J. Birrer, MD, PhD
• Patrick I. Borgen, MD
• Julie R. Brahmer, MD, MSc
• Lior Z. Braunstein, MD
• Adam M. Brufsky, MD, PhD
• Paul A. Bunn Jr, MD
• Howard A. Burris III, MD
• Harold J. Burstein, MD, PhD
• John C. Byrd, MD
• David P. Carbone, MD, PhD
• Arij D’Silva, MD
• Leping Chen, MD, PhD
• Michael A. Choi, MD, MBA
• Ezra Cohen, MD
• Robert L. Coleman, MD
• Raoul S. Concepcion, MD
• E. David Crawford, MD
• Massimo Cristofanilli, MD
• Riccardo Dalla-Favera, MD
• George D. Demetri, MD
• Vincent T. DeVita Jr, MD
• Bernard J. Escudier, MD
• Laura J. Esserman, MD, MBA
• David Michael Euhus, MD
• Alessandra Ferrajoli, MD
• Robert L. Ferris, MD, PhD
• Robert A. Figlin, MD
• Steven E. Finkelstein, MD
• Silvia C. Formenti, MD
• Emil J. Freireich, MD, DSc
• David R. Gandara, MD
• Patricia A. Ganz, MD
• Judy E. Garber, MD, MPH
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• Armando E. Giuliano, MD
• Lori J. Goldstein, MD
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• Leora Horn, MD, MSc
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• Susan Band Horwitz, PhD
• Maha H.A. Hussain, MBChB
• Bruce E. Johnson, MD
• David H. Johnson, MD
• V. Craig Jordan, OBE, PhD, DSc
• Hagop M. Kantarjian, MD
• Philip W. Kantoff, MD
• Beth Y. Karlan, MD
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• Edward S. Kim, MD
• Henry M. Kuerer, MD, PhD
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• Mario E. Lacouture, MD
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• Patrick C. Walsh, MD
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• Howard (Jack) West, MD
• William G. Wierda, MD, PhD
• Eric P. Winer, MD
• Lori J. Wirth, MD
• Jed D. Wolchok, MD, PhD
• W.K. Alfred Yung, MD
• Giants of Cancer Care® Inductee
• Steering Committee Member

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2020 RECIPIENTS

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Past Giants of Cancer Care® Award Winners

2013 Giants
Elizabeth H. Blackburn, PhD
Vincent T. DeVita Jr, MD
Brian J. Druker, MD
Bernard Fisher, MD
Moses Judah Folkman, MD
Lawrence H. Einhorn, MD
Robert A. Kyle, MD
Thomas J. Lynch Jr, MD
Steven A. Rosenberg, MD, PhD
Charles L. Sawyers, MD
Bert Vogelstein, MD

2014 Giants
Kenneth C. Anderson, MD
James P. Allison, PhD
Kie Kian Ang, MD, PhD
Howard A. Burris III, MD
Paul A. Bunn Jr, MD
Riccardo Dalla-Favera, MD
George D. Demetri, MD
Jimmie C. Holland, MD
Hagop M. Kantarjian, MD
Philip W. Kantoff, MD
Edith A. Perez, MD
Janet Davison Rowley, MD
John R. Seffrin, PhD
Dennis J. Slamon, MD, PhD
Patrick C. Walsh, MD
Jedd D. Wolchok, MD, PhD

2015 Giants
Robert C. Bast Jr, MD
Clara D. Bloomfield, MD
Harold P. Freeman, MD
Emil J. Freireich, MD, DSc
Gabriel N. Hortobagyi, MD

2016 Giants
Sir Murray F. Brennan, MD
Samuel Hellman, MD
James F. Holland, MD
John Mendelsohn, MD
Robert J. Motzer, MD
Larry Norton, MD
Joyce A. O’Shaughnessy, MD
Frances A. Shepherd, MD
Jeffrey S. Weber, MD, PhD
Daniel V. Von Hoff, MD

2017 Giants
John L. Cameron, MD
Lewis C. Cantley, PhD
Charles S. Fuchs, MD, MPH
Thomas F. Gajewski, MD, PhD
David R. Gandara, MD
John M. Kirkwood, MD
Hyman B. Muss, MD
Daniel P. Petrylak, MD
Kanti R. Rai, MD
Joseph V. Simone, MD
Herman D. Suit, MD, MSc, PhD
Norman Wolmark, MD

2018 Giants
James O. Armitage, MD
Bart Barlogie, MD
Joseph R. Bertino, MD
Liping Chen, MD, PhD
Laura J. Esserman, MD, MBA
Patricia A. Ganz, MD
Judy E. Garber, MD, MPH
Eli J. Glatstein, MD
Armando E. Giuliano, MD
Wanq K. Hong, MD, DMSc (Hon)
Bruce E. Johnson, MD
V. Craig Jordan, OBE, PhD, DSc
Michael J. Keating, MB, BS
Michael P. Link, MD
Maurie Markman, MD
Caroline Robert, MD, PhD
Richard L. Schilsky, MD
George W. Sledge Jr, MD
Josef Tabernero, MD, PhD
Nicholas J. Vogelzang, MD
W.K. Alfred Yung, MD

2019 Giants
Frederick R. Appelbaum, MD
Bernard J. Escudier, MD
F. Stephen Hodi, MD
Susan Band Horwitz, PhD
David H. Johnson, MD
Beth Y. Karlan, MD
Henry T. Lynch, MD
Richard Pazdur, MD
Charles M. Perou, PhD
Donald P. Pinkel, MD
S. Vincent Rajkumar, MD
Saul A. Rosenberg, MD
Alan P. Venook, MD
Jamie H. Von Roenn, MD
Eric P. Winer, MD

*Posthumous winner
†Deceased

Members of the 2019 class of Giants of Cancer Care® honorees gather during the awards ceremony at the Adler Planetarium in Chicago, Illinois. Back row, from left: Richard Pazdur, MD; Bernard J. Escudier, MD; David H. Johnson, MD; Frederick R. Appelbaum, MD; Charles M. Perou, PhD. Front row, from left: F. Stephen Hodi, MD; Beth Y. Karlan, MD; Eric P. Winer, MD; S. Vincent Rajkumar, MD; Susan Band Horwitz, PhD.

From left: Kenneth C. Anderson, MD; S. Vincent Rajkumar, MD; Kanti R. Rai, MD; and Shaji Kumar, MD, pose for the camera at the 2019 Giants of Cancer Care® awards ceremony.

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ONE
PATIENT
at a time

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Recognize Greatness. Recognize a Giant of Cancer Care.
Cabozantinib Shows Efficacy in HCC With Child-Pugh B Status

by BRITTANY LOVELY

A RETROSPECTIVE ANALYSIS OF data from the CELESTIAL trial has demonstrated a potential role for cabozantinib (Cabometyx) in patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh B liver cirrhosis. This subpopulation of patients is associated with poor prognosis due to advanced cirrhosis of the liver over the course of their disease, said Anthony B. El-Khoueiry, MD, who presented the data during the International Liver Cancer Association (ILCA) 2020 Virtual Conference.

Cabozantinib is approved for patients with advanced HCC who were previously treated with sorafenib (Nexavar) based on data from the CELESTIAL trial (NCT01908426), which recruited patients with Child-Pugh A liver impairment. The median overall survival (OS) for patients treated with cabozantinib (n = 470) was 10.2 months (95% CI, 9.1-12.0) versus 8.0 months (95% CI, 6.8-9.4) in those who received placebo (n = 237; HR, 0.76; 95% CI, 0.63-0.92; P = .005). The median progression-free survival (PFS) was 5.2 months (95% CI, 4.0-5.5) compared with 1.9 months (95% CI, 1.9-1.9) respectively, (HR, 0.44; 95% CI, 0.36-0.52; P < .001). Further, the overall response rates were 4.0% (95% CI, 2.3%-6.0%) and 0.4% (95% CI, 0.0%-2.3%), respectively.

CHILD-PUGH B POPULATION Overall, 10.3% of patients (n = 73) experienced deterioration to Child-Pugh B cirrhosis in the first 8 weeks of the study period, the time of the first Child-Pugh assessment postrandomization. Outcomes evaluated in the retrospective analysis included 51 patients in the cabozantinib arm and 22 patients in the placebo arm who were Child-Pugh B in the study by week 8. Median OS from randomization was 8.5 months versus 3.8 months, respectively (HR, 0.32; 95% CI, 0.18-0.58). Further, the median PFS was 3.7 months versus 1.9 months (HR, 0.44; 95% CI, 0.25-0.76).

“Cabozantinib appears to have a manageable safety profile in this group of patients with comparable dose reduction and discontinuation rates to the overall population,” he said.

FULFILLING AN UNMET NEED Historically, patients with advanced HCC classified with Child-Pugh B are excluded from clinical trials due to an increased mortality rate of approximately 30% compared with 10% for those with Child-Pugh A classification as a result of liver failure. Though understudied in the initial enrollment population, cirrhosis may evolve over the course of treatment in trials for patients with advanced HCC. The analysis of patients who deteriorate following enrollment represents a step forward in fulfilling a considerable unmet need for patients who do not meet historical inclusion criteria.

“The deterioration from Child-Pugh A to Child-Pugh B at week 8 was mostly related to changes from baseline in albumin, bilirubin, and ascites,” El-Khoueiry said. “In the Child-Pugh B subgroup, patients in the cabozantinib arm versus in the placebo arm had higher rates of macrovascular...
invasion, extrahepatic spread, elevated alpha-fetoprotein [≥ 400 ng/mL], and more of the patients had hepatitis B or C etiology for their liver disease.” These rates were, respectively, 43% versus 32%, 82% versus 68%, 39% versus 27%, 35% versus 27%, and 31% versus 18%.1

SAFETY OF CABOZANTINIB IN ADVANCED HCC

“In this subgroup of patients who deteriorated from Child-Pugh A to Child-Pugh B by week 8 [compared with the overall population] we see that they had a similar median duration of exposure to cabozantinib, and they had a similar median average daily dose,” El-Khoueiry said. The median duration of exposure was 3.7 months versus 3.8 months, and the median average daily doses were 36.9 mg versus 35.8 mg, respectively. Of those patients treated with cabozantinib, the rates of dose reductions due to adverse events (AEs) were similar in the Child-Pugh B subgroup (n = 51) and in the safety population of the overall study group (n = 467) with 61% and 62% of patients seeking a lower dose of cabozantinib, respectively. Both populations also experienced a similar rate of discontinuation due to treatment-related AEs (18% vs 16%).

The most common grade 3/4 AEs in the cabozantinib-treated Child-Pugh B subgroup versus the overall population were fatigue (20% vs 10%), ascites (14% vs 4%), aspartate aminotransferase increase (14% vs 12%), and thrombocytopenia (12% vs 3%). Notably, the subgroup experienced lower rates of grade 3/4 palmer-planter erythrodysesthesia (8% vs 17%) and hypertension (8% vs 16%) than the overall population.

“Further prospective studies are warranted in [patients with] Child-Pugh B with HCC, as this is a population with considerable unmet need,” El-Khoueiry said. The safety and efficacy of cabozantinib are being evaluated further in a phase 1/2 trial (NCT04497038) for the treatment of patients with unresectable or metastatic HCC with underlying Child-Pugh B cirrhosis who have either progressed on or were deemed intolerant of first-line systemic therapy.

REFERENCES

Ramucirumab Findings Shed Light on Sequencing Strategies
by RACHEL NAROZNIK, MA

RAMUCIRUMAB (CYRAMZA) was safe and effective as second-line treatment for patients with hepatocellular carcinoma (HCC) who received frontline systemic therapy that did not include sorafenib (Nexavar), according to interim findings presented at the ILCA 2020 Virtual Conference.1

Results from an expansion cohort of the phase 3 REACH-2 trial (NCT02435433) help inform sequencing decisions in HCC, where frontline options have expanded in recent years, Richard S. Finn, MD, said in an interview with OncologyLive®.

Findings from the interim analysis showed that at a median follow-up of 6.5 months, the median progression-free survival (PFS) was 5.5 months (95% CI, 1.3-7.5) with 18 events, which the authors deemed consistent with PFS data observed in patients who received prior sorafenib in REACH-2 (TABLE1,2).

Overall survival (OS) data were immature, with only 10 events reported. At the time of the data cutoff on January 31, 2020, 22 of the 24 patients who received subsequent ramucirumab were off treatment and 2 had died.1 “As of now, all second-line agents approved in HCC have come after prior sorafenib,” Finn said. “We have seen the approvals of lenvatinib [Lenvima] and atezolizumab [Tecentriq]/bevacizumab [Avastin] in the first line. A question that remains to be answered is: How do we best sequence...
Response assessments performed in accordance with RECIST 1.1 criteria indicated that the ORR in the OLE cohort was 16.7% (n = 24), comprised entirely of partial responses. There were no complete responses. The disease control rate was 54.2%, with stable disease observed in 37.5% of patients. Progressive disease (PD) and objective PD were seen in 41.7% of patients each; 4.2% of patients were not evaluable for response.

Data additionally demonstrated that, when compared with baseline values, patients’ albumin-bilirubin (ALBI) scores were preserved during ramucirumab therapy. Investigators measured albumin and bilirubin at baseline and prior to each cycle and calculated participants’ ALBI scores and grades to evaluate liver function throughout the treatment period. The median duration of therapy was 10.50 weeks (interquartile range, 6.00-31.86) and the median number of cycles received was 5.00 (interquartile range, 3.00-14.50). Reasons for treatment discontinuation were varied: 14 because of PD, 4 because of an adverse event (AE), 2 deaths, and 1 each because of physician decision and protocol violation, respectively.

TOXICITIES
Importantly, no deaths due to AEs occurred within 30 days of treatment discontinuation. Most patients (91.7%) experienced 1 or more treatment-emergent AEs (TEAEs) of any grade, while slightly more than half (58.3%) experienced a minimum of 1 grade 3 or grade 4 TEAE. Hypertension, proteinuria, pneumonia, hyponatremia, and ascites represented the 5 most common grade 3 or 4 AEs, affecting 16.7%, 12.5%, 12.5%, 8.3%, and 4.2% of patients, respectively. There were no cases of grade 3 or 4 diarrhea, fatigue, nausea, abdominal distension, decreased appetite, edema, or vomiting.

Regarding TEAEs of special interest (TEAE SI), Finn said no grade 4 or 5 events occurred while patients were receiving ramucirumab. Fifty percent of patients experienced at least 1 TEAE SI; 33.3% reported a minimum of 1 grade 3 TEAE SI. Liver injury/failure was the most prevalent category of grade 3 TEAE SIs (20.8%), followed by bleeding/hemorrhagic events (12.5%). The 5 most prevalent grade 3 TEAE SIs included hypertension (16.7%), proteinuria (12.5%), gastric varices hemorrhage (4.2%), gastrointestinal hemorrhage (4.2%), and ascites (4.2%).

**OLE ELIGIBILITY CRITERIA**
REACH-2, which was the first positive phase 3 trial conducted in a biomarker-selected patient population with HCC, enrolled patients with disease confirmed by histology or radiological imaging which met Barcelona Clinic Liver Cancer staging criteria for stage B or C disease that is refractory or not amenable to locoregional therapy. Patients were also required to have at least 1 untreated target lesion, a Child-Pugh Class A score, an ECOG performance status score of 0 or 1, baseline alpha-fetoprotein of at least 400 ng/mL, and adequate hematologic and biochemical parameters.

**TABLE.** Findings From Pivotal REACH-2 and Expansion Cohort Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Original REACH-2 cohorts</th>
<th>REACH-2 OLE cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ramucirumab plus BSC (n = 197)</td>
<td>BSC (n = 95)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>8.5 (7.0-10.6)</td>
<td>7.3 (5.4-9.1)</td>
</tr>
<tr>
<td>HR (95% CI); P value</td>
<td>0.71 (0.53-0.94); P = .0199</td>
<td>NA</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>2.8 (2.8-4.1)</td>
<td>1.6 (1.5-2.7)</td>
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<tr>
<td>HR (95% CI); P value</td>
<td>0.45 (0.33-0.60); P &lt; .0001</td>
<td>NA</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>4.6% (1.7%-7.5%)</td>
<td>1.1% (0.0%-3.1%)</td>
</tr>
</tbody>
</table>

BSC, best supportive care; NA, not available; OLE, open-label expansion; ORR, overall response rate; PFS, progression-free survival.

For a full list of references, see the article at https://bit.ly/3cnRe9P
Dual Immunotherapy Regimen Boosts Response in HCC

by JASON HARRIS

THE COMBINATION OF TREMELIMUMAB and durvalumab (Imfinzi) improved overall response rate (ORR) and median overall survival (OS) in patients with unresectable hepatocellular carcinoma (HCC) previously treated with sorafenib (Nexavar), according to findings presented during the ILCA 2020 Virtual Conference.

Principal investigator R. Kate Kelley, MD, said results from part 3 of the 4-armed, phase 1/2 Study 22 (NCT02519348) showed that combining the anti-CTLA-4 monoclonal antibody tremelimumab with the anti-PD-L1 monoclonal antibody durvalumab demonstrated efficacy and a tolerable safety profile among patients who were refractory to sorafenib, who had progressed during treatment with the kinase inhibitor, or who had refused sorafenib.

“A single priming dose of tremelimumab combined with monthly durvalumab showed promising clinical activity in a predominantly second-line advanced HCC population,” said Kelley, a gastrointestinal oncologist and associate professor of clinical medicine at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco.

In part 3 of the 3-part Study 22, patients were assigned to a 1-time dose of 300 mg of tremelimumab followed by 1500 mg of durvalumab monthly (T300 plus D; n = 65); the same dose of durvalumab monotherapy (D; n = 64); once-monthly 750 mg tremelimumab monotherapy for 7 doses, then once every 12 weeks thereafter (T; n = 33); or 4 doses of 75 mg tremelimumab plus 1500 mg of durvalumab monthly (T75 plus D; n = 45).

A total of 332 patients were included in parts 2 and 3 of the trial. In the T300 plus D group, 43 patients (57.3%) patients progressed on sorafenib, 12 (16.0%) were refractory, and 20 (26.7%) refused the drug. In the T75 plus D group, those numbers were 47 (56.0%), 10 (11.9%), and 27 (32.1%), respectively. In the D arm, 52 patients (50.0%) patients progressed, 15 (14.4%) were refractory, and 37 (35.6%) refused treatment. In the T arm, those numbers were 30 (43.5%), 14 (20.3%), and 25 (36.2%), respectively.

Kelley noted that the Kaplan-Meier survival curves for patients in part 3 receiving the highest tremelimumab doses, the T300 and tremelimumab monotherapy arms, separated early. The survival advantage in those arms remained consistent through the study period. “The T300 plus D arm had the best performance at the median,” she said.

Median OS in the T300 plus D group was 18.7 months (95% CI, 10.8-27.3), followed by tremelimumab alone (15.1 months; 95% CI, 11.3-20.5), durvalumab alone (13.6 months; 95% CI, 8.7-17.6), and the T75+D group (11.3 months; 95% CI, 8.4-15.0).

Similarly, 18-month survival was greatest in the T300 plus D group (52.0%; 95% CI, 38.9-63.6%), followed by the T arm (45.7%; 95% CI, 32.8-57.7%). The 18-month survival rate was lowest in the D group (35.3%; 95% CI, 25.0%-45.8%) and the T75 plus D group (34.7%; 95% CI, 24.4%-45.2%).

In the T300 plus D arm, ORR was 24.0% (95% CI, 14.9%-35.3%) with 1 (1.3%) complete response (CR) and 17 (22.7%) partial responses (PR). The median duration of response was not reached and the median progression-free survival is 2.17 months (1.91-5.42).

The ORR in the D arm was 16.0% (95% CI, 5.4%-18.1%), followed by 9.5% (95% CI, 4.2%-17.9%) in the T75 plus D arm and 7.2% (95% CI, 2.4%-16.1%) in the T arm. Investigators observed 2 (2.4%) CRs in the T75 plus D arm, and none in the other 2 arms. The median durations of response were 11.2 months, 13.2 months, and 24.0 months, respectively.

Patients from parts 2 and 3 were included in the safety analysis. Investigators did not observe any adverse events (AEs) beyond the known safety profile for any agent. Grade 3/4 treatment-related AEs (TRAEs) were most common in the T arm at 43.5%, followed by the T300 plus D arm at 35.1%, the T75 plus D arm at 23.2%, and the D arm at 17.8%.

There were 17 (24.6%) serious TRAEs, including death, in the T arm; 13 (17.6%) in the T300 plus D arm; 12 (14.6%) in the T75 plus D arm; and 11 (10.9%) in the D arm. Investigators observed 3 (3.0%) deaths due to TRAEs in the D arm, 2 (2.7%) in the T300 plus D arm, and 1 (1.2%) in the T75 plus D arm. There were no deaths due to TRAEs in the T arm.

A total of 30 patients discontinued treatment due to TRAEs, 9 in the T arm, 8 each in the T300 plus D and D arms, and 5 in the T75 plus D arm.

“In sum, these data show that the T300 plus D regimen provides the best benefit-to-risk profile across [treatment] arms,” Kelley said. “Furthermore, the unique association of the T300 plus D regimen with proliferative CD8-positive T cells provides a strong biologic rationale for the observed treatment response, which warrants further study.”

She added that the T300 plus D and monotherapy regimens are being evaluated versus sorafenib for the treatment of HCC in first-line in the ongoing phase 3 HIMALAYA trial (NCT03298451). AstraZeneca, the developer of the agent, hopes to present findings later this year.

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

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION.1,2*

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

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

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

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

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

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

Pre-mEDIATE 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.
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-medicated 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.

FASPRO™ – For a strong start to their treatment journey

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

Contact your Oncology Specialist to learn more about DARZALEX FASPRO™

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.

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
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.

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
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Both systemic administration-related reactions including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO.

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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 [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 a 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: 3 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 3-4 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.

Embryofetal 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 [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 type are not 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 Warning and Precautions].
• Neutropenia [see Warning and Precautions].
• Thrombocytopenia [see Warning 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.

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 39% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fetal adverse reactions occurred in 0.8% of patients.

Permanently discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in <5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia. The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diaphoresis, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
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<tr>
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<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>
| a Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tussisitis, upper respiratory tract infection, and viral pharyngitis.
| b Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.
| c Abdominal pain includes abdominal pain, and abdominal pain upper.
| d Fatigue includes asthenia, and fatigue.
| e Edema peripheral includes edema, edema peripheral, and peripheral swelling.
| f Cough includes cough, and productive cough.
| g Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) include:
• General disorders and administration site conditions: infusion reaction, injection site reaction, chills
• Infections: herpes zoster, urinary tract infection, influenza, sepsis
• Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms
• Nervous system disorders: headache, paresthesia
• Metabolism and nutrition disorders: hypocalcemia, hyperglycemia
• Respiratory, thoracic and mediastinal disorders: dyspnea, pulmonary edema
• Cardiac disorders: atrial fibrillation
Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td></td>
<td>56</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>58</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Fatigue†</td>
<td>52 5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23 2%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18 3%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45 5%</td>
</tr>
<tr>
<td>Constipation</td>
<td>26 2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 0%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection¹</td>
<td>43 3%</td>
</tr>
<tr>
<td>Pneumonia²</td>
<td>23 17</td>
</tr>
<tr>
<td>Bronchitis²</td>
<td>14 2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 0%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31 2%</td>
</tr>
<tr>
<td>Track pain</td>
<td>14 0%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea³</td>
<td>22 3%</td>
</tr>
<tr>
<td>Cough⁴</td>
<td>14 0%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17 2%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 5%</td>
</tr>
</tbody>
</table>

† Fatigue includes asthenia, and fatigue.
‡ Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract infection.
³ Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.
⁴ Fatigue includes asthenia, and fatigue.
⁵ Infusion reactions includes terms determined by investigators to be related to infusion.

Table 4: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>94 34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82 58</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86 9</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>69 52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45 4</td>
</tr>
</tbody>
</table>

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

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>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection⁵</td>
<td>24 1%</td>
<td>22 1%</td>
</tr>
<tr>
<td>Pneumonia⁶</td>
<td>8 5%</td>
<td>10 6%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 1%</td>
<td>11 0.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 0.4%</td>
<td>11 0.4%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue⁷</td>
<td>15 1%</td>
<td>16 2%</td>
</tr>
<tr>
<td>Infusion reactions⁸</td>
<td>13 2%</td>
<td>34 5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 0%</td>
<td>13 1%</td>
</tr>
<tr>
<td>Chills</td>
<td>6 0.4%</td>
<td>12 1%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10 2%</td>
<td>12 3%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough⁹</td>
<td>8 0%</td>
<td>14 0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 1%</td>
<td>11 1%</td>
</tr>
</tbody>
</table>

⁵ 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.
⁶ Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.
⁷ Fatigue includes asthenia, and fatigue.
⁸ Infusion reactions includes terms determined by investigators to be related to infusion.
⁹ Cough includes cough, and productive cough.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) include:
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

Table 6 summarizes the laboratory abnormalities in COLUMBA.

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

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 daily during organogenesis, which is 45 times higher than the human dose.

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

Lactation

Risk Summary

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

Data

Animal Data

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

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 hydrogen bonding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

Usage of daratumumab 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 presence of reversion reactions of M-proteins to lambda.

Treatment-emergent anti-HuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (18/192) 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

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 daily during organogenesis, which is 45 times higher than the human dose.

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

No clinical studies of DARZALEX FASPRO as a combination therapy did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

Adverse events occurring at a higher frequency (≥15% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

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

No clinical studies of daratumumab were 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 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 IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% in 15% to 20%, respectively. The estimated exposure of DARZALEX FASPRO and lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Lenalidomide is only available through a REMS program. Refer to the lenalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal/Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. For fetuses born 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 human immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).
Eprenetapopt May Develop Into New Option for TP53-Mutant MDS

by DENISE MYSHKO

THE ADDITION OF THE experimental small molecule eprenetapopt (APR-246) to a standard treatment for myelodysplastic syndromes (MDS) is showing promise in patients with TP53 mutations, a population that often experiences poor responses to therapy and a high risk of disease progression.1,2

Investigators are testing the combination of eprenetapopt plus azacitidine, a hypomethylating agent, compared with azacitidine alone in patients with TP53 mutations in a phase 3 trial (NCT03745716) (FIGURE).3

Results are expected by the end of 2020 and will be incorporated into new drug applications to the FDA and the European Medicines Agency in 2021, according to Aprea Therapeutics, the company developing the drug.4

Fully enrolled as of June 3, 2020, the trial involves 154 patients in 28 study locations. Participants are expected to receive treatment for an average of 1 year. Results will be stratified by patients’ age (<65 vs ≥65 years). The primary end point is complete response (CR) rate, defined as the proportion of patients who achieve complete remission and duration of CR.

“This is a group that has no good alternatives or good standard of care,” said David Sallman, MD, PhD, principal investigator and assistant member investigator and assistant member in Tampa, Florida. “For example, it’s common for patients with TP53 mutations to have therapy-related disease.”

Demonstrating complete remission is a challenging goal based on the 2006 International Working Group criteria, Sallman added. “Not only do you need blast clearance, which would be the same across myeloid diseases, but you need full count recovery, which means a neutrophil count higher than 1000, a platelet count higher than 100,000, and a hemoglobin [level] higher than 11 g/dL,” Sallman said.

However, he said this is an important measure especially for patients who do not do well on standard therapy. “We and others have shown that complete remission in high-risk MDS is the best biomarker for improvement of overall survival. If the primary endpoint is met, this would support approval of this agent as the first TP53-MDS specific therapy,” he noted.

The study has an open-label design, Sallman said, because the therapies are administered differently. Eprenetapopt is given by infusion over 6 hours over the course of 4 days, whereas azacitidine is given as either a subcutaneous injection or an intravenous infusion.

ROLE OF MUTANT TP53

Overall, TP53 mutations have been observed in an estimated 5% to 10% of patients with de novo MDS/acute myeloid leukemia (AML), which may evolve from MDS, and increase to 25% to 40% of therapy-related MDS/AML. Additionally, these mutations have been identified in 50% of patients with complex karyotypes and in 20% of those with lower-risk MDS with isolated deletion of chromosome 5q.1

The presence of the TP53 mutation has been associated with poor or short responses to intensive chemotherapy, hypomethylating agents, and allogeneic stem cell transplant, according to Thomas Cluzeau, MD, PhD, who presented key findings about eprenetapopt at the 2020 European Hematology Association Virtual Congress in June.1

He heads the Hematology Department at Central University Hospital of Nice in France. TP53 functions as a tumor suppressor gene that, when dysregulated, diminishes antitumor activity and promotes cancer cell growth.

When administered, eprenetapopt is converted into methylene quinuclidinone, which binds to p53 proteins, helping to stabilize and reactivate the protein, according to Aprea Therapeutics.

FIGURE. Eprenetapopt Plus Azacitidine in TP53-Mutant Myelodysplastic Syndromes Phase 3 Trial1

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• MDS diagnoses by WHO criteria</td>
</tr>
<tr>
<td>• Age ≥ 18 years</td>
</tr>
<tr>
<td>• At least 1 TP53 mutation that is not benign</td>
</tr>
<tr>
<td>• ECOG score of 0-2</td>
</tr>
<tr>
<td>• Normal organ function*</td>
</tr>
<tr>
<td>• No prior therapy with hypomethylating agent, intensive chemotherapy, or ASCT</td>
</tr>
<tr>
<td>N = 154 1:1</td>
</tr>
<tr>
<td>Experimental arm</td>
</tr>
<tr>
<td>Eprenetapopt + azacitidine</td>
</tr>
<tr>
<td>Primary end point</td>
</tr>
<tr>
<td>• Complete response rate</td>
</tr>
<tr>
<td>Control arm</td>
</tr>
<tr>
<td>Azacitidine</td>
</tr>
</tbody>
</table>

*Defined as creatinine clearance >30 mL/min; total serum bilirubin <1.5 x ULN or total bilirubin ≥3.0 x ULN or greater; and ALT and AST <2.5xULN.
**RESULTS FROM EARLIER STUDIES**

The rationale for combining eprenetapopt and azacitidine in patients with TP53-mutant MDS has been established in findings from 2 early-phase trials conducted in the United States and France.

In a phase 1b/2 study (NCT03072043), the combination was evaluated in 55 patients: 40 had MDS; 11 had AML with myelodysplasia-related changes, and 4 had chronic myelomonocytic leukemia/MDS-myeloproliferative neoplasms.

Overall, the combination was well-tolerated with high response rates in both MDS and AML. Sallman and colleagues said in presenting the results at the 2019 American Society of Hematology Annual Meeting.

After a median follow-up of 10.5 months, the overall response rate (ORR) was 87%, including a 53% CR rate. Among those with MDS, the CR rate was 61%. Median time to response for the entire population was 2.1 months. In the intention-to-treat (ITT) population, median overall survival (OS) was 11.6 months (95% CI, 9.2-14.0) with significantly longer OS in responding patients (12.8 vs 3.9 months; \(P < .0001\)).

These outcomes compare favorably to CR rates of approximately 20% and a median OS of 7 to 8 months typically seen in this population with standard-of-care hypomethylating agents, investigators indicated.

Treatment-related adverse effects (AEs) included nausea/vomiting (58%), dizziness (31%), constipation (24%), neuropathy (22%), leukopenia (22%), and thrombocytopenia (20%). All were grade 1 or 2, except for cytopenias. Treatment-related febrile neutropenia occurred in 9% of patients and anemia occurred 5% of patients.

No patient discontinued therapy because of treatment-related AEs, Sallman said, adding that the more severe AEs seen are what would normally occur with azacitidine alone. “The only unique toxicity is a neurologic change that occurs during the infusion, which includes a tremor, altered sensation, or unsteadiness, but that resolves after the completion of the infusion,” he said.

The phase 2 French study (NCT03588078), conducted by Groupe Francophone des Myelodysplasies, enrolled patients with TP53-mutated MDS or AML who were treated with the eprenetapopt plus azacitidine combination.

Participants received 4500 mg/day of intravenous eprenetapopt over 6 hours on days 1 to 4 and 75 mg/m² of subcutaneous azacitidine on days 4 to 10 every 28 days for 6 cycles.

Patients who responded to the combination continued on therapy until relapse. Patients were recommended for allogeneic stem cell transplant, if appropriate, after 3 to 6 cycles of study therapy and were eligible afterward for continued therapy at reduced doses. In the ITT population, the ORR was 62% among patients with MDS (n = 34), including a 47% CR rate; 64% among those with AML with 20% to 30% blasts (n = 11), including a 27% CR rate; and 29% for those with AML with greater than 30% blasts (n = 7), with no CRs.

Among evaluable patients who received at least 3 cycles of therapy and had a marrow evaluation after 3 cycles, the ORR was 75% in the MDS cohort (n = 28) with a 57% CR; 78% for the AML 20% to 30% blast group (n = 9), with a 33% CR; and 100% in the AML over 30% blast group (n = 2), with no CRs.

In the ITT population, the median OS was 12.1 months (95% CI, 8.9-15.3) for both the entire group (n = 52) and for the MDS cohort after a median follow-up of 9.7 months. Median OS was 13.0 months (95% CI, 5.4-22.5) for the AML 20% to 30% blast group and 3.0 months (95% CI, 0.6-6.5) for those with greater than 30 blasts.

For patients who remained on treatment for 3 or more cycles, the median OS was higher at 13.7 months (95% CI, 11.7-15.7) versus 2.8 months (95% CI, 1.2-4.4) for patients who were on treatment for fewer than 3 cycles (\(P < .0001\)).

Overall, all-grade AEs included febrile neutropenia in 19 patients (37%), and 21 patients (40%) experienced neurologic AEs, including ataxia (n = 13) cognitive impairment (n = 4), acute confusion (n = 4), isolated dizziness (n = 3), and facial paresthesia (n = 1).

**FUTURE DEVELOPMENT**

Eprenetapopt has received breakthrough therapy, orphan drug, and fast track designations from the FDA for MDS, as well as orphan drug status from the European Union for MDS, AML, and ovarian cancer.

In addition to the pivotal MDS study, Aprea Therapeutics is sponsoring a phase 2 trial (NCT03931291) assessing eprenetapopt plus azacitidine in patients with TP53-mutant MDS or AML who have received an allogeneic stem cell transplant to evaluate the regimen as posttransplant maintenance therapy. The study, which has a target enrollment of 31 patients, has a primary endpoint of relapse-free survival at 12 months.

Other ongoing trials include a phase 1 study testing eprenetapopt plus azacitidine and venetoclax (Venclexta) in TP53-mutant myeloid malignancies (NCT04214860) and a phase 1/2 study of eprenetapopt in combination with pembrolizumab (Keytruda) in solid malignancies (NCT04383938).
**INDICATION**

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

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

**IMPORTANT SAFETY INFORMATION**

**Pneumonitis** occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of interstitial lung disease (ILD)/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

**Hypertension** occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

**Hepatotoxicity:** Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased AST occurred in 69% of patients, including Grade 3/4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

**Impaired wound healing** can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

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

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

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

**Please see Brief Summary of full Prescribing Information for GAVRETO on adjacent page.**

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

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

Hypertension
Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on severity.

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Hemorrhagic Events
Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Interstitial Lung Disease/Pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic Events
- Risk of Impaired Wound Healing

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET altered solid tumors in ARROW. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

RET Fusion-Positive Non-Small Cell Lung Cancer
The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW. The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino. Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients; fatal adverse reaction which occurred in > 1 patient included pneumonia (n = 3) and sepsis (n = 2).
Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

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

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

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

Table 4 summarizes the adverse reactions in ARROW.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=220</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue¹</td>
<td>35</td>
<td>2.3*</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Edema²</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>Diarrhea³</td>
<td>24</td>
<td>3.2*</td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain⁴</td>
<td>32</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension⁵</td>
<td>28</td>
<td>14*</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough⁶</td>
<td>23</td>
<td>0.5*</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia⁷</td>
<td>17</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

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

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 83 to 94 patients.

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

**DRUG INTERACTIONS**

**Effects of Other Drugs on GAVRETO**

**Strong CYP3A Inhibitors**

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

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

**Strong CYP3A Inducers**

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

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Table 5 summarizes the laboratory abnormalities in ARROW.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>69</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>42</td>
</tr>
<tr>
<td>Decreased alkaline phosphtase</td>
<td>40</td>
</tr>
<tr>
<td>Increased calcium (corrected)</td>
<td>29</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>27</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>54</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>52</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 83 to 94 patients.
USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Females

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

Males

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

Infertility

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

Pediatric Use

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

Animal Toxicity Data

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

Geriatric Use

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

Hepatic Impairment

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

by JASON HARRIS

MAINTAINING SEXUAL FUNCTION IS often low on the list of priorities for a woman recently diagnosed with a gynecologic cancer, but raising the subject early in her treatment course may make the patient more willing to engage in a discussion as her care progresses, according to Don S. Dizon, MD, who specializes in survivorship issues.

Patients and their partners will remember that the physician initiated the conversation, Dizon said in an interview with OncologyLive®. He added that discussing sexual function is important so that a patient knows there are no limits to what she can talk about with her physician. The physician, he said, leaves the door open until the patient is ready to walk through it.

“It may not be the case that a woman whom you’re asking, ‘Would you like to discuss sexual health at this time?’ is going to go into the extreme details of her intimate sex life, but it might be [the case] months down the road,” said Dizon, director of women’s cancers at Lifespan Cancer Institute, and clinical director of gynecologic medical oncology and director of medical oncology for Rhode Island Hospital, both in Providence.

“When the smog clears from a cancer diagnosis, they may be able to say, ‘You know what? I don’t know how to be intimate with my partner now.’ It’s really important that they understand and recognize that this is a legitimate cause for their concern and that we are here to give them hope,” he said.

Dizon said it can be difficult to discuss this topic with patients, as oncologists often have little or no training in discussing sex and sexual health. Furthermore, physicians may have biases that lead them to assume, for instance, that a woman over 60 years may no longer be interested in sex, or that a lesbian might not be interested in penetrative sex. Dizon added that sex is a “delicate topic,” and the patient may be as unwilling to discuss what she does in the bedroom as the physician is uncomfortable to hear it.

He pointed out, however, that physicians have no trouble discussing with patients the nausea, diarrhea, and vomiting that may result from cancer therapy. “Those are not exactly delicate topics that you’re going to want to bring up in regular conversations,” Dizon said. “And I think, for the same way, we need to start being frank about sexual health and how our treatments would [affect] them. Most of our patients will get better once they have the conversation.”

FINDING AVAILABLE RESOURCES

Dizon advised physicians to develop skills for talking with patients about sexual function and to embrace the topic as a part of routine medical practice. He also encouraged physicians to seek out resources and experts, both externally and within their own institutions, who can help guide patients.

“You need to give patients permission to bring it up,” he said. “We do know from the data that most patients are going to look for cues from their providers that this is a safe area to bring up. They’re not just going to randomly, spontaneously, talk about their sex lives.”

Most advocacy organizations, particularly those that focus on breast cancer, have information available for patients and their loved ones about sexual function issues and restarting their sexual lives after cancer therapy, Dizon said. For adolescent and young adult survivors, the Young Survival Coalition’s Living Beyond Breast Cancer program and Stupid Cancer, in particular, provide information on intimacy and dating.

He also mentioned Will2Love.com, a website for men and women developed by Leslie R. Schover, PhD, whom he described as “one of my mentors” in the field. “It is a self-exploratory website filled with anecdotes and case scenarios, and also information that can empower people to recover, but at their own pace,” Dizon said.

Schover is a clinical psychologist and internationally recognized expert on sexual problems and infertility related to cancer treatment. Dizon serves as a scientific advisor to Will2Love, which works with patients and health care providers to address sexual health concerns and chronic illness.

At Lifespan Cancer Institute, Dizon started the Sexual Health First Responders Clinic to provide personalized, multidisciplinary consultation and treatment for sexual health issues that patients with cancer encounter. The “first responder” aspect of the clinic gives other physicians a place to refer patients who need help.

Dizon also worked with Areej El-Jawahri, MD, a specialist in hematologic malignancies, to develop a sexual health program at Massachusetts General Hospital in Boston for patients who had undergone hematopoietic stem cell transplant. El-Jawahri and colleagues demonstrated that if a pilot program in which patients’ needs were assessed, education was provided, and therapeutic intervention, if appropriate, was offered, this would result in improvements to sexual function, quality of life, and mood.

Nevertheless, Dizon said patients and physicians should not have to depend on having access to in-house expertise for information. Valid information should be available, both online and in the literature, so that people can access the latest data wherever they are, he said.

“Education is exceptionally valuable for anyone who’s having issues related to sexual dysfunction after cancer,” he said. “Having people understand that this is not something they’re going through alone, that a lot of people have issues with sexual health and intimacy and body image after treatment of cancer, makes it feel less isolating as an issue. When people finally get to understand what’s happened and what’s happening, that’s another way to gain control of the situation.”

REFERENCE

The recent approvals of fam-trastuzumab deruxtecan-nxki (Enhertu) and tucatinib (Tukysa) are evidence that the HER2-positive breast cancer treatment paradigm is continuously evolving, according to Debu Tripathy, MD.

On December 20, 2019, the FDA granted an accelerated approval to the antibody-drug conjugate (ADC) trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti–HER2-based regimens in the metastatic setting. The approval provides an alternative to standard-of-care ado-trastuzumab emtansine (T-DM1; Kadcyla) in later lines of therapy, Tripathy said.

“There are certain characteristics of trastuzumab deruxtecan that are distinct from T-DM1. In the laboratories and preclinical models, trastuzumab deruxtecan is water soluble. When it’s internalized into the tumor cell, it’s slowly released into the microenvironment and can diffuse back out of the cells,” Tripathy explained. “It may even be able to impact neighboring cells, which is very important. I believe that after progressing on T-DM1 and receiving trastuzumab deruxtecan instead, we may not go back to T-DM1.”

There have been additional paradigm-shifting efforts in 2020. On February 25, 2020, the FDA expanded the approval for neratinib (Nerlynx) to encompass its use in combination with capecitabine for adults with advanced or metastatic HER2-positive breast cancer who were previously treated with a minimum of 2 anti–HER2-based regimens in the metastatic setting.

Tucatinib followed suit shortly thereafter, receiving approval on April 17, 2020, for use in combination with trastuzumab (Herceptin) plus capecitabine in adults with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received 1 or more prior anti–HER2-based regimens in the metastatic setting.

In an interview with OncologyLive®, Tripathy, professor and chairman of the Department of Breast Medical Oncology in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston, discussed recent additions to the HER2-positive breast cancer armamentarium and how to best sequence them.

How has an evolving understanding of the role of HER2 in breast cancer affected the development of new therapies? Certain cancers are driven by genetic abnormalities that result in protein characteristics, such as the expression of the HER2 receptor, in this case. These characteristics continue to be important drivers, even as the tumor may evolve through different stages of resistance. We have found that every single treatment we use in HER2-positive breast cancer, upon serial progression, is targeting HER2 in one way or another. [HER2] still remains a viable target; [therapeutic advancements are] just a matter of targeting it in a different manner.

Two new therapies have [recently] been approved. One is an ADC [trastuzumab deruxtecan], which targets HER2. The toxic moiety is actually a chemotherapy drug; it’s not specific to HER2. The other one is a kinase inhibitor [tucatinib] that specifically inhibits the HER2 kinase domain. In fact, it’s the only HER2-specific kinase inhibitor; the others inhibit EGFR. These have yielded significant and notable differences, particularly in refractory/resistant breast cancer. These drugs generated a lot of enthusiasm, and many more are in the pipeline.

What is the optimal sequence of therapies for patients with HER2-positive breast cancer? For patients with unchanged, first-line, HER2-positive metastatic breast cancer who are presenting with de novo metastatic disease or have already received adjuvant or neoadjuvant trastuzumab, after 1 year, first-line therapy has not changed. It typically [consists of] a taxane, most commonly docetaxel, although others use paclitaxel, with trastuzumab and pertuzumab [Perjeta]. That is still our standard first-line therapy.

Second-line therapy is also relatively standard. We’re still using T-DM1 on the basis of the EMILIA [NCT00829166] and TH3RESA [NCT01419197] studies, whose results showed superiority over lapatinib [Tykerb] and capecitabine, which are second-line therapies that we have used before. Now, looking forward, second-line therapy may change, with ongoing second-line trials assessing therapies beyond T-DM1.

The third-line setting is a little open right now. There are 2 drugs that can be used in that setting and partly depend on what patients have previously received. The regimen of tucatinib, trastuzumab, and capecitabine, which are second-line therapies that we have used before, now, looking forward, second-line therapy may change, with ongoing second-line trials assessing therapies beyond T-DM1.

Sequencing is based on a few factors. The first consideration is the level of evidence. For example, tucatinib has a higher level of toxicity based on the phase III TKI301 study [NCT02486585] and on the findings of the phase III MONARCH study [NCT02486585]. The second consideration is the toxicity profile of the agents, especially with regard to irinotecan and T-DM1’s safety profiles differ? The agents each have distinct toxicities, but this may also guide treatment paradigms. There are going to be trials that move trastuzumab deruxtecan up into earlier lines of therapy. There will also be head-to-head comparisons against T-DM1. We should get a better understanding of how these drugs work.

1. Q How do trastuzumab deruxtecan and T-DM1’s safety profiles differ?
The main questions are ‘How does this translate clinically?’ and ‘What is the human immune system actually seeing, and how well is it reacting?’ The SOPHIA trial [NCT02492711] results showed that it does seem to be making a difference.

The clinical difference is not that great in terms of progression-free and overall survival, but nonetheless, it’s important. I believe it may have a role in later lines of therapy. Some of the ongoing studies may pinpoint patients who benefit more [from margetuximab] than others. I believe that continuing to refine this whole concept is an important area. Other bispecific antibodies that engage the immune system are being tested right now. This whole field is ripe for advances, but I clearly believe there will be a role [for margetuximab] perhaps in later lines of therapy.

Better drugs. It’s clear that under selective pressure, you do get additional mutations. Even the RAS pathway can now exhibit mutations particularly in patients on hormone therapy and those who have HER2-positive and hormone receptor-positive disease. We will [see] more of these niche trials with rare populations of patients. They will require collaboration on a national and global level for enrollment.

**Have there been therapeutic developments specifically for patients with leptomeningeal disease?**
Yes. Leptomeningeal disease remains a very difficult disease to treat. In HER2-positive disease, there are some interesting trials. There is one currently open through the Translational Breast Cancer Research Consortium [in which investigators are evaluating] tucatinib, trastuzumab, and capecitabine [NCT03501979], which is essentially the same regimen tested in the HER2CLIMB trial [NCT02614794].

There are some data from the large randomized trial on CNS and even some pilot data on a few patients with leptomeningeal disease. That is an ongoing study. We also have other approved drugs that are specifically for patients with brain metastases, which we sometimes use in leptomeningeal disease. For example, the combination of neratinib and capecitabine is one [regimen] that is active. The National Comprehensive Cancer Network lists it as a treatment just for CNS disease, but it can also be used for leptomeningeal disease.

**What is the rationale for exploring genomically guided therapy in patients with HER2-positive breast cancer and brain metastases?**
I believe that genomically guided therapy can be used for any patient. Whether or not brain metastases are present, *genomically directed therapy* is a broad phrase. There are many ways you can interpret that one, for example, when you’re targeting a specific mutation. One of the more common druggable mutations that we see in HER2-positive breast cancer is PIK3CA mutations. About 25% of HER2-positive cancers harbor this mutation.

There are ongoing trials combining PI3K inhibitors with trastuzumab monotherapy or trastuzumab plus pertuzumab. For example, there is a large, ongoing study [NCT04208178] evaluating alpelisib [Piqray] and trastuzumab plus pertuzumab in the maintenance phase after induction therapy in the first-line setting. We’re going to learn more about genomically targeted therapies.

We know that CDK4/6 inhibitors now have shown improvements when combined with HER2-targeted therapy. Therefore, that is another area that is ripe for exploration. I do believe that as we learn more about the genomic landscape of HER2, we will find
evidence, which was shown in a phase 3 randomized trial that demonstrated a survival difference. On the other hand, with trastuzumab deruxtecan, we are still awaiting the phase 3 data. The phase 2 data were notable because patients were heavily pretreated. This may be an option to save for later.

The final issue is the toxicity. Even though it’s very rare, the problems with interstitial lung disease can be fatal. Of course, this is something to factor in as well. There is also the presence of central nervous system [CNS] disease, which may pivot you more toward tucatinib because of its demonstrated activity in the brain. This makes sense because it’s a small molecule inhibitor and, as with capecitabine, the CNS [penetration] may be a little higher.

That is how we make clinical judgments regarding which agents to use in the third-line setting. Of course, whatever you don’t use in the third-line setting can be used in the fourth-line setting. It’s not uncommon for our patients with advanced HER2-positive disease to do well and to have good performance statuses on later lines of therapy.

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**How might margetuximab be integrated into a patient’s treatment course, presuming FDA approval?**
That’s hard to say. Margetuximab is a very interesting drug in theory because of the way it was designed. The idea of being an engineer to better augment and interact with the immune system is something that has been thought about for a long time. For more than a decade, we’ve recognized that the immune system plays an important role in the response of HER2-positive breast cancers, especially when using antibodies. The antibody that is approved is [immunoglobulin G1], which has the ability to engage T cells and effector cells.

Therefore, the binding of the fragment crystallizable region of the antibody to these effector cells can be variable because individuals inherit different versions of the receptors. [Margetuximab] is engineered in a way that binds the fragment crystallizable region more tightly to immune components. This has been demonstrated in preclinical models.
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**:0.83 (95% CI: 0.76-0.90); P<0.001†

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 complication. 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 or 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 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 <60 mL/min. No dose adjustments were made, and no doses 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. 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.

‡P value for superiority.

Deviation from standard XGEVA® Q4W demonstrated an increased rate of bone complications

- 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)§**
  - 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>
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<td><strong>31%</strong></td>
<td><strong>61%</strong></td>
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Incidence of bone complications (N=29) | Incidence of bone complications (N=31)

Dosing was considered once every 27-30 days in this study. 1

**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. 3

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 above 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 metastasis 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.
Palliative Care Can Address Gaps in Oncology Landscape

by QUAN T. DANG, MD; AND LYDIA MILLS

PALLIATIVE MEDICINE HAS EVOLVED to become a standard for high-quality cancer care, helping patients relieve suffering throughout their journey, improving quality of life (QOL), and prolonging survivorship. Palliative care providers can address issues related to treatment adherence, unrecognized symptoms, financial issues, and caregiver burden.

Guidelines from the American Society of Clinical Oncology (ASCO) recommend integrating palliative care into oncology care. Providing patients with this service can help oncology practices excel in the value-based world, but many community practices struggle with implementing this specialty. However, some viable, cost-effective strategies can allow practices of all sizes to offer these valuable services.

CHALLENGES OF ADDING PALLIATIVE SERVICES

Reimbursement is the most significant obstacle practices face when trying to offer palliative care. Many palliative services are time intensive, so these specialists cannot see as many patients in a day as the average provider. Consequently, they cannot fully pay for themselves in a fee-for-service (FFS) model. The financial value of what they offer is the savings from reduced resource utilization at the end of treatment, when costs are highest.

Large organizations can redirect resources from bundled payment programs or other initiatives such as the Oncology Care Model (OCM) to fund these extra services. In fact, 94% of hospitals with more than 300 beds and 72% of hospitals with more than 50 have palliative care beds.

Unfortunately, this is not an option for smaller or most medium-size community practices or those in rural areas, because they simply do not have access to the same level of funding as larger practices.

Even though health care is transitioning to value-based care, most of the services physicians provide are still reimbursed by FFS. With this structure, it is challenging for many practices, especially those in a community setting, to develop their own palliative care programs.

Staffing is also an issue. Training capacity is insufficient to keep up with population growth and demand for palliative care services. Currently, there is just 1 palliative care physician per 1200 people who have a serious illness in the United States. In oncology specifically, there is just 1 palliative care physician per 141 oncologists.

Research suggests that by 2030, just 1 palliative care physician will be available for every 26,000 patients. Similar shortages are predicted for nurses, social workers, and spiritual care providers with training in palliative care.

Lastly, changing the mindset of some oncologists and adjusting practice workflows can be problematic. Palliative care is a relatively new field, and some physicians who have not had exposure to this specialty may lack an understanding of the benefits these services provide. Additionally, established workflows are difficult to alter.

A WEALTH OF BENEFITS

Providing expert and timely symptom management for patients with high symptom burden improves a patient’s QOL and satisfaction. The findings of 1 study of patients with non–small cell lung cancer revealed that early palliative care led to improvements in QOL and mood, as well as increased survival by an average of nearly 3 months. In another study at a cancer care center, results showed fewer hospital admissions and emergency department visits and reduced intensive care unit use, as well as lower direct costs of inpatient care in the last 6 months of life.

Palliative care services can also be a differentiating factor in the market, positioning the practice as a leader in palliative medicine. Physicians benefit, as well, because they can focus more on treating the patient’s disease rather than managing symptoms.

Study findings show that palliative medicine reduces the cost of care. The most recent study to add to this growing body of evidence measured the total cost of care (TCOC) for patients with cancer who received less than 3 days of hospice care at the end of life compared with those who received 3 days or more. The study, conducted by researchers across The US Oncology Network, analyzed 7329 deaths that occurred with patient who had Medicare and were enrolled in the OCM who died while under the care of practices in the network. The results reinforce previous studies regarding TCOC in the last 30 days of life, finding that dying in the hospital cost twice as much as dying at home under hospice care ($20,113 vs $10,803).

Palliative care enhances survivorship by
liberating patients from suffering, providing a better QOL, and allowing more access to an oncologist. Unfortunately, there is an ongoing misunderstanding of what palliative care is and when patients should start receiving these services. Because many think it pertains only to the very end of life, it is essential to educate providers and patients about the benefits of early intervention.

Ideally, a connection with a palliative care specialist should occur at the time of diagnosis so that the road to survivorship is as smooth as possible. Today there is a greater awareness of the value of these services in oncology, and the need is growing. Changing paradigms in delivery reimbursement and virtual technology are leading to increased access, enabling many more patients to have the best possible experience during their cancer journey.

**ESTABLISHING BEST PRACTICES**

Ideally, cancer centers have an in-house (embedded) program. At a minimum, their interdisciplinary palliative care team should include a dedicated physician, nurse, and social worker. Other key specialists include dietitians, chaplains, counselors, pharmacists, rehabilitation specialists, and physical therapists. Offering these services in-house is ideal for patients because it provides better communication, continuity of care, and focused mission.

In-house providers can access palliative care specialists practically anywhere via virtual technology. These specialists can provide actual supportive care services, as well as guidance and mentorship. Some practices in the network with numerous sites have plans underway to use technology to bring palliative care to their locations that do not have access to these resources. This approach is also viable for small or medium centers with limited funding. Expensive diagnostic video equipment is not necessary for a high-quality encounter.

Another option is to partner with other palliative medicine specialists. In most communities, cancer centers can partner with palliative medicine specialists and organizations to provide seamless palliative care services. Hospice is always a good choice, offering skilled specialists who can provide these services in addition to traditional hospice care. Academic institutions make good partners because they have vast resources, enabling them to offer a wide range of services. Many hospital systems also provide these services, as do some insurance companies.

Recognizing the funding obstacles encountered when adding palliative care, The US Oncology Network has taken an innovative approach to solving the problem by developing a nurse practitioner (NP) program model. A pilot program underway in several practices across the network uses NPs who are certified in palliative care and social workers who have expertise in the field. Program costs are much lower because it is built around NPs rather than physicians. Medical oncologists do play a role in prescribing medications, but their time commitment is minimal. This model enables practices to start a program on a smaller scale and, based on volume, slowly grow it until there is justification for hiring a physician.

One practice that has piloted a palliative care program is Oncology Hematology Care (OHC) in Cincinnati, Ohio. Two NPs received training in palliative care in the summer of 2019, and the organization implemented its program in October 2019. To prepare for this launch, OHC created symptom pathways and note templates in the emergency medical record and provided education about palliative care and the program to physicians, nurses, navigators, and the front desk staff. The practice targeted all patients with stage IV disease and with pancreatic and brain tumors. They started with 2 palliative care appointments each week per advanced practice provider. By February 2020, they were offering palliative care in 3 of their regions.

Another member of the network, New York Oncology Hematology (NYOH) in Albany, had an NP start seeing patients in palliative care earlier this year, working with a medical oncologist, as a pilot. NYOH also partnered with an outside palliative care program and worked closely with an NP and a social worker (both certified in palliative care). The program was successful enough that NYOH decided to embed it into their practice, and the NP and social worker joined NYOH in July.

Ellen Gokey, director of palliative care at NYOH, said they are focusing on following metrics, including discussion and documentation of advanced directives, time from diagnosis to time of referral to palliative care, pain management, and hospice referrals.

“We will also be focusing on initiatives to decrease hospital admissions and emergency room visits by focusing on symptom management,” she said. “Our goal is to continue to educate providers and staff regarding the importance of incorporating palliative care earlier in the disease trajectory in order to establish a trusting relationship with the patients and work on improving their quality of life while they are receiving disease-modifying treatment. We will be providing palliative care in all of our locations and hope to continue to add to the team to incorporate [members from] other disciplines who are also certified in palliative care.”

Quan T. Dang, MD, is a palliative medicine physician with Texas Oncology, a practice in The US Oncology Network, and Lydia Mills is a senior manager of palliative care and social work at McKesson.
HHS Releases Plan to Strengthen Rural Health Care

by KEITH A. REYNOLDS

THE US DEPARTMENT OF Health & Human Services (HHS) has released its Rural Action Plan, the first department-wide assessment of rural health care efforts in 18 years. The plan will serve as a road map for the department to strengthen coordination among agencies in order to better serve rural communities across the country.¹

There are 57 million people living in rural areas of the United States, spread over 80% of the country’s landmass, according to the HHS plan. In 2018, HHS funded approximately $8 billion in individual grants that went directly to rural communities.

“Growing up in rural Maryland, I saw first-hand some of the challenges faced by rural health care providers and patients,” HHS Secretary Alex Azar said in a news release on September 3.² “We have invested unprecedented time and resources transforming health care for the forgotten men and women of rural America. The Rural Action Plan identifies key tangible areas where HHS agencies can soon make a real difference in the health outcomes of millions of Americans.”

People living in rural areas face challenges in access to care, financial viability, and demographic and structural issues. They may be older and in poorer health. People who live in rural areas are more likely to die from cancer and other diseases, such as heart disease, chronic lower, respiratory disease, and stroke than their urban counterparts, and to face challenges related to limited and varied health services, the report indicated.

Over the past 18 months, the HHS Rural Task Force sought the input of rural stakeholders, state governors, and members of Congress. For example, research has shown that people with disabilities have unique and greater challenges compared with the general rural population and people with disabilities in urban areas.

The plan examines the challenges facing rural communities, including emerging health disparities, chronic disease burden, high rates of maternal mortality, and limited access to mental health services. It includes a 4-point strategy to transform rural health services.

The first point of the plan is to build a sustainable health and human services model for rural communities. It includes actions such as:

- funding the Rural Healthcare Providers Transition Project, a new program to provide support for hospitals and rural health clinics transitioning to value-based models;
- expanding the Community Health Aide Program, which provides education and training of tribal community health providers to increase access to quality health care, health promotion, and disease prevention services; and
- funding the Integrated Rural Community Care project to connect federally qualified health centers with rural hospitals to better coordinate preventive, primary, and emergency health care.

The second point of the plan involves technology and innovation. It includes as follows:

- supporting a new HHS Health Challenge to leverage technology to improve screening and management of postpartum depression for rural women;
- providing more than $8 million in funding for the Telehealth Network Grant Program to provide emergency care consults via telehealth to rural providers without emergency care specialists; and
- developing new flexibility for Medicare Advantage (MA) plans to improve access to managed care options in rural areas through changes in network adequacy assessments for MA plans and to take into account the impact of telehealth providers in contracted networks.

The third point focuses on preventing disease and mortality, and includes:

- creating the Healthy Rural Hometown Initiative, which will identify strategies to address the growing rural disparities related to the 5 leading causes of avoidable death: stroke, heart disease, cancer, respiratory disease, and injury/substance use;
- investing more than $2 million in additional funding for rural cancer control grants with a focus on geographically underserved rural areas with deep and/or persistent poverty, building on a multiyear research effort to increase prevention efforts and enhance cancer treatment efforts in rural communities; and
- investing more than $2 million in funding in 2020 as part of a 4-year, $8 million project to identify evidence-based interventions that can reduce health risks faced by Americans in rural areas.

The final point is to increase rural access to care. It includes:

- issuing a new policy brief examining the workforce shortage challenges that state-based licensure restrictions create for residents of rural areas by failing to let health care clinicians practice to the full extent of their training;
- investing $5 million in fiscal year 2020 to recruit and train emergency medical services personnel in rural areas; and
- awarding $8.25 million to 11 communities that develop new programs through the Rural Residency Planning and Development Program.

With regard to addressing inequities in cancer care, the plan calls for administrative supplements for the National Cancer Institute (NCI). Specifically, NCI is targeting $2 million in fiscal year 2020 for 10 administrative supplements in geographically underserved areas.

In fiscal year 2021, the NCI will invest $3 million to support research focused on preventing cancer and addressing risk factors of those in rural areas. This research will focus on social determinants of health and behavioral risk factors, as well as the barriers that contribute to cancer disparities.

REFERENCES
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Expert Speakers

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Stony Brook University

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New Framework for Genetic Testing in Prostate Cancer Takes Shape

by KERRY R. SCHAFFER, MD

IN RECENT YEARS, great progress has been made in understanding the genetics of metastatic prostate cancer which has translated into the development of new precision therapies. The FDA has approved 2 PARP inhibitors—rucaparib (Rubraca) and olaparib (Lynparza)—for use in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) defects.1,2 Pembrolizumab (Keytruda), a checkpoint inhibitor, is also approved for use in solid malignancies with mismatch repair deficiency (dMMR), microsatellite instability (MSI), or high tumor mutational burden (TMB).3 More than 20% of patients with mCRPC have HRR defects or dMMR on somatic tumor testing,4 and 12% reflect germline mutations.5 

Given the high proportion of patients with actionable mutations, somatic testing is now an important standard of care for patients with metastatic prostate cancer.6 Additionally, national guidelines state that all men with metastatic prostate cancer and some men with localized prostate cancer qualify for germline testing.7 With increased genetic testing in metastatic prostate cancer, questions arise regarding the optimal biopsy site, timing, and type of testing to offer, and the interpretation of results. While no universal protocol has been established, data from recent studies can be used to create a framework for implementation of genetic testing.

SELECTING PATIENTS FOR TESTING

National Comprehensive Cancer Network guidelines indicate that all men with metastatic prostate cancer qualify for somatic and germline testing, regardless of family history, age of cancer onset, indolent/aggressive nature of metastatic disease, or race. Initial prostate cancer genomic studies reflected data from predominantly Caucasian populations.4,5 However, recent studies demonstrate that the prevalence of germline and somatic mutations and genomic signatures that impact clinical decisions are not significantly different between racial groups. These include, but are not limited to, alterations in BRCA1/2, ATM, TMB, and MSI status.6,10 With higher prostate cancer incidence and mortality in African Americans compared to other racial groups, there is national recognition of the need to improve access to care for minorities;11 and genetic testing must be included in this strategy.

WHAT TO LOOK FOR IN SOMATIC TESTING REPORTS

Somatic features that qualify patients with metastatic prostate cancer for precision therapies include pathogenic mutations in HRR genes (eg, BRCA1/2, ATM), dMMR (eg, MSH2, MSH6, MLH1, PMS2), MSI-high status, or high TMB (≥ 10 mut/Mb). Treating providers should ensure that the test report specifically comments on these but also can review the report for other noteworthy findings such as variants of uncertain significance mutations in actionable genes that may be reclassified over time, genetic alterations suggestive of an incidental hereditary cancer syndrome,12 and mutations for which there is evolving knowledge regarding prognostication (eg, SPOP, WNT, MHC).13 It may be helpful to review these more nuanced findings at local or regional genitourinary or molecular tumor boards.

SOMATIC TESTING SAMPLES: PRIMARY VERSUS METASTATIC SITE

HRR mutations, if present, are usually identified in prostate specimens in paired primary-metastatic studies, reflecting an early alteration.14 The PROfound trial (NCT02987543) identified a similar prevalence of actionable HRR mutations between different tissue types: archived primary (27.1%), archived metastatic (33.2%), new primary (28.9%), and new metastatic (29.5%).15 In this study, the majority of specimens (89.9%) were archived; rates of sequencing success were 63.9% for new versus 56.9% for archived specimens (FIGURE).16 This study also highlighted potential barriers to successful testing including decalcification technique of osseous biopsies, low tumor fraction, and older sample age. The proportion of samples on which somatic testing can successfully be performed declines over time, likely as tissue quality is compromised. Peripheral blood sampling for circulating tumor DNA (ctDNA) testing is convenient; however, if possible, a solid tumor biopsy is preferable to ctDNA, as ctDNA is not always entirely concordant with the tumor tissue genomes.17,18 If ctDNA is used, the highest yield would be at disease progression when considering precision therapies in patients with mCRPC and higher tumor burden.19

WHEN TO SEND SOMATIC TESTING

Ideally, all patients will be offered somatic testing prior to decline in function that prohibits further therapy. Each biopsy can subject patients to financial burden, possible...
Partner Perspectives

discomfort, and additional medical appointments. Therefore, when possible, efforts should be made to use previously acquired tissue that may yield therapeutic information. Data from the PROfound trial demonstrate that both primary and metastatic sites can be used for testing. Thus, it is reasonable to offer testing on a prostate specimen or adequate site of metastatic biopsy at the time of metastatic prostate cancer diagnosis, increasing the likelihood that previously acquired tissue can be used, potentially avoiding subsequent biopsies.

For patients without an existing adequate biopsy at the time of hormone sensitive metastatic prostate cancer diagnosis, obtaining a biopsy at the time of mCRPC is warranted. Delaying somatic testing until mCRPC will maximize the potential of identifying actionable acquired mutations; most commonly these are ATM or dMMR.

Finally, if actionable mutations are not identified on initial somatic testing, repeat biopsy for retesting should be considered for heavily treated patients. This may identify a mutation that had a false-negative or an acquired actionable mutation or genomic signature. While dMMR and MSI-high status are rare (approximately 3%), in select patients immunotherapy can provide tremendous benefit.

WHY IS GENETIC TESTING IMPORTANT?

Although only a proportion of patients have actionable mutations, offering somatic testing to all patients with metastatic prostate cancer is imperative, as it can reveal precision therapy options. If a gene alteration is identified on somatic testing and a hereditary cancer syndrome is suspected, offering germline testing with formal genetic counseling is warranted. It is important to stress that a somatic testing result without pathogenic mutations in a negative formal germline test because depth of coverage and techniques of sequencing vary across the different platforms. In addition to somatic testing, all patients with metastatic prostate cancer should be informed of their eligibility for formal germline counseling and testing.

Ultimately, patient-provider discussions regarding testing, tissue availability and quality, disease presentation, cost, and patient willingness to undergo biopsy all play into the implementation of somatic testing. When these factors come together effectively, the result is an improved, personalized approach to treatment. Although genetic testing in metastatic prostate cancer can be complex, the results benefit patients and, in some cases, their relatives as well. The use of genetic testing will likely continue to grow as knowledge of genetic vulnerabilities and drivers of prostate cancer continue to advance.

FIGURE. Tissue Testing Success Rates in the PROfound Trial

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archived tissue</td>
<td>56.9%</td>
</tr>
<tr>
<td>Newly collected tissue</td>
<td>63.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor sample location</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor tissue</td>
<td>56.3%</td>
</tr>
<tr>
<td>Metastatic tumor</td>
<td>63.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Collection method</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core needle biopsy</td>
<td>52.4%</td>
</tr>
<tr>
<td>Incisional biopsy</td>
<td>53.6%</td>
</tr>
<tr>
<td>Excisional biopsy</td>
<td>61.5%</td>
</tr>
<tr>
<td>TURP</td>
<td>69.8%</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>74.0%</td>
</tr>
<tr>
<td>Trephine biopsy</td>
<td>86.7%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ tissue site</th>
<th>Success Rate</th>
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</thead>
<tbody>
<tr>
<td>Bone</td>
<td>42.6%</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>56.2%</td>
</tr>
<tr>
<td>Liver</td>
<td>56.3%</td>
</tr>
<tr>
<td>Lung</td>
<td>60.5%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>74.7%</td>
</tr>
<tr>
<td>Other, not specified</td>
<td>74.8%</td>
</tr>
</tbody>
</table>

TURP, transurethral resection of the prostate.
NEDD8 Emerges as a Novel Target in Hematologic Malignancies

by JANE DE LARTIGUE, PHD

INVESTIGATORS ARE DEVELOPING a new way to target a key oncogenic mechanism that may prove to be an effective anticancer strategy, particularly against hematologic malignancies.

Pevonedistat (MLN4924) is the first drug directed at the NEDD8-activating enzyme (NAE) to reach later-stage clinical development. Emerging phase 2 data demonstrating pevonedistat’s particular promise in patients with higher-risk myelodysplastic syndromes (HR-MDS), a form of the disease for which outcomes are still poor, were presented at several conferences this year and have drawn attention to this drug’s unique mechanism of action.1,2

The neddylation pathway that pevonedistat targets is a close relative of the ubiquitin-proteasome system (UPS), which is responsible for the degradation of most intracellular proteins and is vital for the maintenance of cellular homeostasis.3 Cancer cells are highly dependent on a functional UPS.4

Starting in 2003 with the approval of bortezomib (Velcade) for patients with multiple myeloma, the major strategy for targeting the UPS has been through inhibiting the proteasomes that play a central role in the pathway.5,6

Although 2 other proteasome inhibitors (PIs), carfilzomib (Kyprolis) and ixazomib (Ninlaro), are now part of the therapeutic repertoire for multiple myeloma, the approved indications for these drugs have not expanded beyond this cancer type, and the utility of the PI class overall is hindered by toxicity.3,4,7,8

Pevonedistat’s target, NAE, catalyzes the first step in the UPS pathway through an enzymatic cascade that “tags” protein substrates with the ubiquitin-like molecule NEDD8 and feeds into the UPS to facilitate the degradation of a subset of cellular proteins, including tumor suppressors (FIGURE).6,9-11

This approach is showing early signs of success. Pevonedistat, given in combination with the hypomethylating agent azacitidine, has advanced to phase 3 clinical trials in MDS (PANTHER; NCT03268954) and acute myeloid leukemia (AML; PEVOLAM; NCT04090736). In July 2020, the FDA granted pevonedistat a breakthrough therapy designation for HR-MDS. Meanwhile, pevonedistat may also have potential in other types of hematologic malignancies and solid tumors.12-15

THE UBIQUITIN-PROTEASOME SYSTEM

The UPS, a major system of intracellular protein breakdown, is responsible for the degradation of up to 80% of cellular proteins through coordinated activity of the 26S proteasome and a small protein, ubiquitin.3

The 26S proteasome is a multisubunit protease complex that breaks down proteins into smaller peptides. Proteins to be degraded are tagged with multiple ubiquitin molecules via an enzymatic cascade involving an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligase.4,7,8

Evidence that cancer cells have amplified dependence on the UPS, likely because of their increased metabolic demands and need to protect against apoptosis, has provoked interest in drugs targeting the UPS.4,7

The major focus has been on PIs. The 3 currently approved PIs all target the 20S core particle of the proteasome and broadly inhibit proteasome activity. Targeting the proteasome is challenging because of its essential role in cellular homeostasis, which is reflected in the toxicity associated with these drugs.3,4,7,8

PIs have proved particularly effective in patients with multiple myeloma, a cancer of the immunoglobulin-producing plasma cells. Myeloma cells produce large amounts of misfolded immunoglobulin, which is toxic to the cell unless degraded by the UPS.8 However, the success of PIs has not been replicated in other hematologic malignancies or solid tumors, with the exception of bortezomib’s approval in mantle cell lymphoma.3,5,7,8

ALTERNATIVES TO UPS TARGETS

To develop drugs with less toxicity and greater efficacy across a broader spectrum of tumor types, investigators have begun to look for more cancer-specific ways to block UPS activity.3

NEDD8 is a ubiquitin-like molecule that is conjugated to a target protein substrate via neddylation, an enzymatic cascade that closely resembles ubiquitination. The neddylation pathway begins with NAE, the sole NEDD8 E1, which activates NEDD8 in an ATP-dependent manner.9,11,16

An NAE-NEDD8 complex is then transferred to 1 of the 2 E2 NEDD8-conjugating enzymes, UBE2F and UBE2M. The final step involves an E3 NEDD8 ligase, the best characterized of which are RBX1 and RBX2, which facilitate covalent attachment of NEDD8 to a lysine residue within the target protein.9,11,16

Unlike ubiquitination, neddylation does not directly target proteins for proteasomal degradation.8 Instead, it controls the activity, cellular localization, stability, or conformation of its substrates. Nonetheless, the neddylation pathway indirectly contributes to the proteasomal degradation of a critical subset of cellular proteins through its effects on cullin-RING ligases (CRLs)9,11,16

CRLs, the largest family of E3 ubiquitin ligases, are multiprotein complexes that control the degradation of about 20% of all cellular proteins via the UPS. Cullins, which function as scaffold proteins within the CRL complex, are the best-known neddylation substrates. Neddylation is required for activation of CRLs, and the proteins degraded by activated CRLs influence many vital biological processes.9,11,16

Although generally much less well characterized, some non-cullin proteins are also targets of neddylation. A notable example is the tumor suppressor p53, whose neddylation is catalyzed by the E3 ligation MDM29,11,16

In its dual role as both an E3 ubiquitin ligase and an E3 NEDD8 ligase, MDM2 can facilitate both the ubiquitination and
neddylation of p53, respectively. The former leads to p53 degradation, whereas the latter inhibits its transcriptional activity.\textsuperscript{9,11,16}

Studies have demonstrated that NEDD8 and many components of the neddylation pathway are overexpressed across different types of human cancer, including glioblastoma and lung, liver, esophageal, nasopharyngeal, and colorectal cancers. Furthermore, this overexpression has been shown to correlate with disease progression and poorer prognosis. Currently, immunohistochemical staining to measure levels of neddylation enzymes and global NEDD8-conjugated proteins can be used to determine the neddylation status of a tumor. In the future, neddylation status may prove useful as a biomarker predicting patient response to therapy; however, its use is currently restricted to the research setting.\textsuperscript{9,11}

**PEVONEDISTAT: A FIRST-IN-CLASS NAE INHIBITOR**

Components of the broader UPS beyond the 20S core particle represent a host of potentially druggable targets. Although many inhibitors of these targets have been tested in preclinical research, few have advanced to clinical trials.\textsuperscript{3} Agents targeting NAE, the E1 neddylation enzyme, represent a rare exception.

Pevonedistat potently and specifically inhibits NAE activity, and in a variety of cancer cell lines derived from solid tumors and hematologic malignancies, it was shown to block cullin neddylation, which inhibited activation of CRLs. This protected CRL substrates from UPS-mediated degradation, causing their accumulation, ultimately leading to a number of cellular outcomes, including induction of cell death and cell cycle arrest.\textsuperscript{9,17-20}

In xenograft tumor models, including those derived from melanoma and colon, lung, liver, pancreatic, and ovarian cancers, pevonedistat displayed potent antitumor activity and was well tolerated. Furthermore, it was shown to have synergistic activity with a range of anticancer therapies.\textsuperscript{9,11,13,15}

A report of synergy between pevonedistat and azacitidine in a preclinical model of AML\textsuperscript{21} formed the rationale for combining the 2 agents in a phase 1 clinical trial in patients with AML (NCT01814826). Sixty-four patients aged 60 or older with treatment-naive AML unfit for standard induction therapy were treated with pevonedistat at 20 mg/m\textsuperscript{2} or 30 mg/m\textsuperscript{2} as an intravenous infusion on days 1, 3, and 5 and azacitidine at 75 mg/m\textsuperscript{2} on days 1 to 5, 8, and 9 of 28-day cycles.

The overall response rate (ORR) in the intention-to-treat (ITT) cohort was 50%, including 20 complete remissions (CRs), 5 CRs with incomplete hematologic recovery (CRi), and 7 partial remissions. The median duration of remission was 8.3 months. The most common treatment-emergent adverse events (AEs) were constipation, nausea, fatigue, and anemia. Dose-limiting toxicities (DLTs) included elevated transaminase and bilirubin levels, and 20 mg/m\textsuperscript{2} was chosen as the recommended phase 2 dose for pevonedistat.\textsuperscript{22}

Data from the phase 2 Pevonedistat-2001 trial (NCT02610777) were recently presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program and the Virtual European Hematology Association Annual Congress.\textsuperscript{1,2} This open-label, randomized trial

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**FIGURE.** Structure of the Proteasome and the Ubiquitin-Proteasome System\textsuperscript{6,9-11}
enrolled patients with HR-MDS/chronic myelomonocytic leukemia, defined as Revised International Prognostic Scoring System risk greater than 3, or low-blast AML. Patients (N = 120) who were ineligible for stem cell transplant and had not previously received hypomethylating drugs were randomized to receive 28-day cycles of azacitidine (75 mg/m²) on days 1 to 5, 8, and 9 alone or in combination with pevonedistat (20 mg/m²) on days 1, 3, and 5.

Although not statistically significant, a trend toward improvement in overall survival (OS) was observed in the pevonedistat arm in both the ITT population (21.8 months vs 19.0 months; HR, 0.80; P = .334) and in subgroups of patients with HR-MDS (23.9 months vs 19.1 months; HR, 0.70; P = .240) and low-blast AML (23.6 months vs 16.0 months; HR, 0.49; P = .081). Notably, the study was not powered to detect a difference in OS because it was originally a secondary end point.

In addition, investigators noted a significant improvement in event-free survival (EFS; time from randomization to death or transformation to AML) in patients with HR-MDS in the pevonedistat arm (20.2 months vs 14.8 months; HR, 0.54; P = .045); EFS also trended longer in the ITT population (21.0 months vs 16.6 months; HR, 0.65; P = .060).

In the overall response-evaluable population, the ORR was 71% in the combination arm compared with 60% with azacitidine alone, and the CR plus CRi rate was 46% and 38%, respectively. Among patients with HR-MDS, 52% of those treated with pevonedistat achieved CR compared with just 27% of those in the monotherapy arm (P = .050).

The AE profiles of the combination and azacitidine monotherapy arms were comparable; grade 3 or higher AEs occurred in 90% and 87%, respectively, with the most common being neutropenia (31% vs 27%), febrile neutropenia (26% vs 29%), anemia (19% vs 27%), and thrombocytopenia (19% vs 23%). Patient-reported health-related quality of life was similar in the 2 arms, and fewer on-study deaths occurred with the combination (9% vs 16%).

DLTs associated with pevonedistat are often related to hepatotoxicity, including elevated levels of bilirubin and transaminases. Rare deaths have occurred as a result of multiorgan failure and sepsis.13-15,22,23

OTHER TUMOR TYPES

Several other phase 1 clinical trials have evaluated pevonedistat at escalating doses with various dosing schedules. Among 55 response-evaluable patients with AML treated with pevonedistat monotherapy, the ORR was 13% (NCT00911066).2 Results of a trial of 42 patients with relapsed/refractory multiple myeloma or lymphoma (NCT00722488) included 3 partial responses (PRs); an additional 30 patients achieved stable disease (SD).13

Trials examining pevonedistat in nonhematologic malignancies have demonstrated some activity in patients with metastatic melanoma. Among 37 response-evaluable patients, 1 had a PR and 15 achieved SD. In 4 of those patients, SD lasted for at least 6.5 months (NCT01011530).14

Recently, pevonedistat in combination with platinum-based chemotherapy showed potential in patients with advanced solid tumors (NCT01862328). Patients were treated in 21-day cycles with escalating doses of pevonedistat starting at 15 mg/m² on days 1, 3, and 5. Pevonedistat was combined with docetaxel 75 mg/m² (arm 1) or carboplatin target area under the concentration-time curve of 5 mg/ mL/min plus paclitaxel 175 mg/m² (arm 2), both on day 1. Patients were also enrolled in arm 3 evaluating pevonedistat in combination with gemcitabine, but this regimen was abandoned because of toxicity.

Among 19 evaluable patients in arm 1, the ORR was 16% (all PRs); responders included patients with cholangiocarcinoma and head and neck cancer. There was an ORR of 35% in arm 2, with 8 of 23 evaluable patients achieving PR or complete response, including patients with bladder and endometrial cancers. The median duration of response was 5.9 months in both arms.12

This study also explored the expression of the ERCC1 protein as a potential biomarker of response. A component of the nucleotide excision repair (NER) DNA repair pathway, ERCC1 is thought to be involved in resistance to platinum-based chemotherapy.12 In a lung cancer model, pevonedistat was shown to synergize with platinum-containing chemotherapy by interfering with the NER pathway. By preventing cells from using this pathway to repair platinum-induced genetic lesions, pevonedistat promotes the buildup of DNA damage that drives tumor cells to apoptosis. Thus, pevonedistat might resensitize tumors to platinum-based chemotherapy by counteracting the ERCC1/NER-mediated mechanism of resistance.12,23

ERCC1 expression was assessed using a semiquantitative algorithm that incorporates immunohistochemical staining intensity and the percentage of stained cells to calculate a “histoscore,” or H-score.24 Among 21 ERCC1-evaluable patients, those with high ERCC1 levels (H-score greater than the median of 170) tended to remain on study longer and experience greater clinical benefit than patients with low ERCC1 levels (H-score ≤ 170).12

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

For a full list of references, see the article at OncLive.com.
QUAZAR® AML-001

The efficacy of ONUREG® was evaluated in QUAZAR® AML-001, a multicenter, randomized, double-blind, placebo-controlled, phase III study. Eligible patients were ages 55 years or older, had AML, and were within 4 months of achieving first complete remission (CR) with intensive induction chemotherapy. A total of 472 patients who completed induction with or without consolidation therapy were randomized 1:1 to receive ONUREG® 300 mg (n=238) or placebo (n=234) orally on Days 1 to 14 of each 28-day treatment cycle. Efficacy was established on the basis of overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to ONUREG® compared with placebo. In the trial, ONUREG® showed a median OS of 24.7 months (95% CI: 18.7, 30.5) vs 14.8 months (95% CI: 11.7, 17.6) for patients receiving placebo (HR 0.69 [95% CI: 0.55, 0.86]).

ONUREG® is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

Embryo-Fetal Toxicity
ONUREG® can cause fetal harm when administered to a pregnant woman. Azacitidine caused fetal death and anomalies in pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mg/m² basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG® and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG® and for at least 3 months after the last dose.

Serious adverse reactions occurred in 15% of patients who received ONUREG®. Serious adverse reactions in ≥2% included pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG®.

Most common (≥10%) adverse reactions with ONUREG® vs placebo were asthenia (44%, 25%), constipation (39%, 24%), pneumonia (27%, 17%), abdominal pain (22%, 13%), arthralgia (14%, 10%), decreased appetite (13%, 6%), febrile neutropenia (12%, 8%), dizziness (11%, 9%), pain in extremity (11%, 5%).

There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG® and for at least 3 months after the last dose.

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

ONUREG® (azacitidine) tablets, for oral use

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

INDICATIONS AND USAGE
ONUREG (azacitidine) is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

DOSAGE AND ADMINISTRATION
Important Administration Information
Do not substitute ONUREG for intravenous or subcutaneous azacitidine. The indications and dosing regimen for ONUREG differ from that of intravenous or subcutaneous azacitidine [see Warnings and Precautions].

Recommended Dosage
The recommended dosage of ONUREG is 300 mg orally once daily with or without food on Days 1 through 14 of each 28-day cycle. Continue ONUREG until disease progression or unacceptable toxicity.

Administer an antiemetic 30 minutes prior to each dose of ONUREG for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.

If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on Day 1 of a cycle, do not administer ONUREG. Delay the start of the cycle until the ANC is 0.5 Gi/L or more.

Instruct patients on the following:
• Do not split, crush, or chew ONUREG tablets.
• Take a dose about the same time each day.
• If a dose of ONUREG is missed, or not taken at the usual time, take the dose as soon as possible on the same day, and resume the normal schedule the following day. Do not take 2 doses on the same day.
• If a dose is vomited, do not take another dose on the same day. Resume the normal schedule the following day.

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

Monitoring and Dosage Modifications for Adverse Reactions
Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression.

The recommended dosage modifications for adverse reactions are provided in Table 1.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression [see Warnings and Precautions]</td>
<td>Neutrophils less than 0.5 Gi/L on Cycle Day 1</td>
<td>• Interrupt treatment. Resume at the same dose once neutrophils return to 0.5 Gi/L or higher.</td>
</tr>
<tr>
<td></td>
<td>Neutrophils less than 1 Gi/L with fever at anytime</td>
<td>First Occurrence • Interrupt treatment. Resume at the same dose once neutrophils return to 1 Gi/L or higher. Occurrence in 2 Consecutive Cycles • Interrupt treatment. After neutrophils return to 1 Gi/L or higher, resume at reduced dose of 200 mg. • If a patient continues to experience febrile neutropenia after dose reduction, reduce the treatment duration by 7 days. • If febrile neutropenia reoccurs after dose and schedule reduction, discontinue ONUREG.</td>
</tr>
<tr>
<td></td>
<td>Platelets less than 50 Gi/L with bleeding</td>
<td>First Occurrence • Interrupt dose. Resume at the same dose once platelets return to 50 Gi/L or higher. Occurrence in 2 Consecutive Cycles • Interrupt dose. After platelets return to 50 Gi/L or higher, resume at reduced dose of 200 mg. • If a patient continues to experience thrombocytopenia with bleeding after dose reduction, reduce the treatment duration by 7 days. • If thrombocytopenia with bleeding reoccurs after dose and schedule reduction, discontinue ONUREG.</td>
</tr>
<tr>
<td>Gastrointestinal Toxicity [see Adverse Reactions]</td>
<td>Grade 3 or 4 Nausea or Vomiting</td>
<td>• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 Diarrhea</td>
<td>• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.</td>
</tr>
</tbody>
</table>

Table 1: Recommended Dosage Modifications for Adverse Reactions (Continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions]</td>
<td>Grade 3 or 4</td>
<td>• Interrupt dose and provide medical support. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity re-occurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG (azacitidine).</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS
ONUREG is contraindicated in patients with known severe hypersensitivity to azacitidine or its components [see Adverse Reactions and Description (11) in full Prescribing Information].

WARNINGS AND PRECAUTIONS
Risks of Substitution with Other Azacitidine Products
Due to substantial differences in the pharmacokinetic parameters [see Clinical Pharmacology (12.3) in full Prescribing Information], the recommended dose and schedule for ONUREG are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG may result in a fatal adverse reaction. Treatment of patients using ONUREG at the doses recommended for intravenous or subcutaneous azacitidine may not be effective.

Do not substitute ONUREG for intravenous or subcutaneous azacitidine [see Dosage and Administration].

Myelosuppression
New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG, respectively. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia, respectively. Less than 1% of patients discontinued ONUREG due to either neutropenia or thrombocytopenia.

Monitor complete blood counts and modify the dosage as recommended [see Dosage and Administration]. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes
In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodyplastic syndromes were randomized to ONUREG or placebo. One-hundred and seven patients received a median of 5 cycles of ONUREG 300 mg daily for 21 days of a 28-day cycle. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in patients who received ONUREG compared with placebo. The most frequent fatal adverse reaction was sepsis. The safety and effectiveness of ONUREG for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG is not recommended outside of controlled trials.

Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal dose less than the recommended dose and schedule resulted in a developmental toxicity similar to that observed in animals at a maternal dose of 200 mg. Based on the mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal dose less than the recommended dose and schedule resulted in a developmental toxicity similar to that observed in animals at a maternal dose of 200 mg.

Adverse reactions which required an interruption of ONUREG in > 5% of patients included neutropenia (20%), thrombocytopenia (11%), and nausea (11%). Interruptions of ONUREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which resulted in permanent discontinuation of ONUREG in > 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%). Interruptions of ONUREG due to an adverse reaction occurred in 5% of patients. Adverse reactions which resulted in permanent discontinuation of ONUREG in > 1% of patients included neutropenia (20%), thrombocytopenia (8%), and anemia (6%). Dose reductions of ONUREG due to an adverse reaction occurred in 14% of patients. Adverse reactions which required a dose reduction in > 1% of patients included neutropenia (6%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%). The most common (> 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity. Table 2 summarizes the adverse reactions in QUAZAR.
Table 2: Adverse Reactions (≥ 5%) in Patients with AML Who Received ONUREG (azacitidine) with a Difference Between Arms of ≥ 2% Compared to Placebo in QUAZAR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONUREG (N=236)</th>
<th>Placebo (N=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Infections</td>
<td>27</td>
<td>9</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

a Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain.  
b Grouped term includes fatigue and asthenia.  
c Broad scope term includes influenza, pneumonia, respiratory tract infection, respiratory tract infection viral, bronchopulmonary aspergillosis, lung infection, Staphylococcus infection, atypical pneumonia, lower respiratory tract infection, lung abscess, Pneumocystis jiroveci pneumonia, pneumonia bacterial, pneumonia fungal, Pseudomonas infection, hemoptysis, productive cough, pleural effusion, atelectasis, pleural pain, rales, Enterobacter test positive, and Hemophilus test positive.

Clinically relevant adverse reactions that did not meet criteria for inclusion in Table 1 were weight decreased (4%) in patients who received ONUREG. Neutropenia, thrombocytopenia, and anemia of any grade occurred in 74%, 65%, and 25% of patients treated with ONUREG. Table 3 summarizes select Grades 3 or 4 hematological laboratory abnormalities in QUAZAR.

Table 3: Selected Hematological Laboratory Abnormalities That Worsened from Baseline in Patients Who Received ONUREG in QUAZAR

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ONUREG</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Grade 0-2</td>
<td>Post-Baseline Grade 3 or 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>223</td>
<td>109 (49)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>222</td>
<td>46 (21)</td>
</tr>
<tr>
<td>Anemia</td>
<td>229</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of intravenous or subcutaneous azacitidine. 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.

- Hypersensitivity reaction
- Intestinal lung disease
- Tumor lysis syndrome
- Sweet’s syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome

USE IN SPECIFIC POPULATIONS

Gastrointestinal Toxicity

Advise patients of the risk of gastrointestinal toxicity with ONUREG and of the potential need to use anti-emetic or anti-diarrheal medications during treatment [see Adverse Reactions].

Embryo-Fetal Toxicity

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

Infertility

Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose.

Infertility

Based on animal data, ONUREG may impair male or female fertility [see Nonclinical Toxicology (13.1) in full Prescribing Information].

Pediatric Use

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

Geriatic Use

Of the 238 patients in QUAZAR who received ONUREG, 72% were 65 years of age or older, while 12% were 75 years or age of older. No overall differences in safety or effectiveness of ONUREG were observed between these patients and younger patients.

Renal Impairment

Monitor patients with severe renal impairment (creatinine clearance [Clcr] ≤ 15 mL/min calculated by Cockcroft-Gault formula) more frequently for adverse reactions and modify the ONUREG dosage for adverse reactions [see Dosage and Administration].

No dose adjustment of ONUREG is recommended for patients with mild to severe renal impairment (Clcr > 1.5 to ≤ 3 mL/minute).

Hepatic Impairment

ONUREG has not been studied in patients with pre-existing severe hepatic impairment (total bilirubin > 3 × ULN). A recommended dosage of ONUREG has not been established for patients with moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3 × ULN). No dose adjustment of ONUREG is recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN) or total bilirubin 1 to 1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) in full Prescribing Information].

PATIENT COUNSELING INFORMATION

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

Myelosuppression

Advise patients of the risk of myelosuppression with ONUREG and of the need to monitor complete blood counts before and during treatment [see Warnings and Precautions].

REFERENCES


Manufactured by:
Celgene Corporation
A Wholly Owned Subsidiary of Bristol-Myers Squibb
90 Morris Avenue
Summit, NJ 07901

ONUREG® is a registered trademark of Celgene, a Bristol-Myers Squibb Company.

ONUR.001 September 2020

ONU_HCP_BSv.001 09/2020

Bristol Myers Squibb™
AN INCREASED UNDERSTANDING of the biologic intricacies of acute myeloid leukemia (AML) has led to the identification of more than 100 driver mutations associated with the disease, opening the door for targeted therapies with clinically meaningful outcomes for patients who are not candidates for intensive chemotherapy regimens.1

AML is 1 of the most deadly and difficult cancers to treat. Chemotherapy remains the treatment mainstay for most patients; however, for those who experience an initial response, refractory disease is common.

Additionally, patients may not be candidates for induction chemotherapy because of fitness status, which includes factors such as age, performance status, and comorbidities.

During a recent OncLive Peer Exchange®, a panel of experts in leukemia discussed therapies that are reshaping the AML treatment landscape for some of the most vulnerable patient subsets.

They highlighted the use of the BCL-2 inhibitor venetoclax (Venclexta) in combinations as well as the emergence of the epigenetic drugs ivosidenib (Tibsovo) and enasidenib (Idhifa) for patients with IDH mutations. In addition to providing an overview of the clinical trial data for these drugs, they shared their insights into how they are using these agents in clinical practice and addressing treatment-related adverse events (AEs) to maximize outcomes.

**VENETOCLAX: A NEW STANDARD OF CARE**

In November 2018, the FDA granted accelerated approval to venetoclax for use in combination with the hypomethylating agents (HMAs) azacitidine (Vidaza) and decitabine (Dacogen) or with low-dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adults aged at least 75 years or those with comorbidities that preclude the use of intensive induction chemotherapy.2 Approval was based on data from 2 open-label nonrandomized trials: M14-358 (NCT02203773), which assessed venetoclax in combination with azacitidine (n = 67) or decitabine (n = 13), and M14-387 (NCT02287233), which assessed venetoclax in combination with LDAC (n = 61), including in patients previously treated with an HMA for an antecedent hematologic disorder.

In these studies, 37% (n = 25) of those receiving venetoclax plus azacitidine achieved complete remission (CR), with a median of 5.5 months in remission; 54% (n = 7) of those receiving venetoclax plus decitabine achieved CR, with a median of 4.7 months in remission; and 21% (n = 13) of those receiving venetoclax plus LDAC achieved CR, with a median time in remission of 6 months.2

“Most of us who treat AML have been very excited these past couple of years to see what venetoclax can do for some patients,” Daniel Pollyea, MD, MS, said. However, he noted that approval was based on phase 2 data in noncomparative studies, which is why data in a randomized setting were highly anticipated. “Most of us who have worked in AML know this is a critical test,
a time when a lot of prior therapies have not been able to surmount this challenge in a randomized setting," he said. Pollyea proceeded to discuss the randomized, phase 3 VIALE-A (NCT02993523) and VIALE-C (NCT03069352) studies, which evaluated venetoclax in combination with azacitidine or LDAC, respectively.

VIALE-A Study
The VIALE-A study randomly assigned 431 treatment-naïve patients with confirmed AML who were ineligible for standard induction therapy because of age (≥ 75 years), comorbidities, or both 2:1 to azacitidine plus venetoclax (n = 286) or azacitidine plus placebo (n = 145). At a median follow-up of 20.5 months, the median overall survival (OS) was 14.7 months in the venetoclax arm and 9.6 months in the placebo arm (HR for death, 0.66; 95% CI, 0.52-0.85; P < .001). The venetoclax arm also had a significantly higher incidence of CR compared with the placebo arm (36.7% vs 17.9%; P < .001), including composite CR (CR or CR with incomplete hematologic recovery; 66.4% vs 28.3%; P < .001).

"Most of us who treat this disease were relieved and very happy to see the data for the venetoclax arm. [The agent] really performed very consistently with what we have come to expect, based on the phase 2 data. Those of us who have been using this agent frequently in the past year and a half, based on the approval, are reassured that this likely is the new standard of care in this setting," Pollyea said. Throughout the discussion, the other panelists agreed that clinicians should consider venetoclax plus azacitidine the new standard of care for patients with AML who are not candidates for induction therapy because of age or comorbidities.

"We’ve been stuck in 28% to 30% response land for older patients with AML for decades. Now that’s not true. The 60% or greater response rates across cytogenetic groups, across molecular groups, are real. They happen. They’re quick. You don’t have to wait for 100 cycles of azacitidine to see those responses. It’s usually after 1 cycle, sometimes 2," Gail J. Roboz, MD, said.

Based on the VIALE-A data, moderator Harry Paul Erba, MD, PhD, noted that "HMA monotherapy should not even be considered for our patients anymore." He also explained that almost two-thirds of US patients, half of whom are aged at least 65 years, have historically not undergone AML treatment because of the relative lack of OS benefit seen with HMA monotherapy. In such untreated patients with AML, he said, the median survival is approximately 2 months, but with venetoclax plus azacitidine, older patients can have a median OS of 15 months. "[Subsequently], it’s not 15 months versus 9 or 10 months; it’s 15 months versus 2 months. We have to get away from the therapeutic nihilism in older patients with AML. In fact, the greatest survival benefit is seen in those over the age of 75 years," he said.

VIALE-C Study
The VIALE-C study randomly assigned 211 treatment-naïve patients with confirmed AML who were ineligible for standard induction therapy because of age (≥ 75 years), comorbidities, or both 2:1 to LDAC in combination with venetoclax (n = 143) or placebo (n = 68). In the primary analysis, at a median follow-up of 12 months, the venetoclax arm had a 25% reduction in the risk of death, with a median OS of 7.2 months compared with 4.1 months in the placebo arm, a finding that did reach statistical significance (P = .04). However, after a median follow-up of 17.5 months, the venetoclax arm demonstrated a 30% reduction in the risk of death, with a median OS of 8.4 months versus 4.1 months in the placebo arm, a finding that did reach statistical significance (P = .04).4

"Based on a press release and some other information, [we had] the impression that the study would not be positive when compared with low-dose cytarabine alone. [But] when patients were followed for a little longer than the original planned analysis, there was a survival benefit," Pollyea said. He noted several reasons why the VIALE-C study may have shown less OS benefit than the VIALE-A study, such as the inclusion of a more challenging patient population. He noted that more than 33% of patients in the study had previously received an HMA for a myelodysplastic syndrome, and such patients had been excluded from the VIALE-A study. Regardless, Pollyea said the most important takeaway is that this regimen provides another treatment option. "For us in the leukemia world, there’s no way that’s not a good thing."

Roboz, who was a coauthor of the VIALE-C study, said that although the findings are overshadowed by the azacitidine data, LDAC plus venetoclax is still a useful regimen. "The reason you’re not seeing the benefit is more because of disadvantageous study design with respect to the hazard ratio and statistics rather than because the regimen doesn’t have any benefit," she said. Although venetoclax plus azacitidine is taking its place as the new standard of care, Roboz said she would still try LDAC plus venetoclax for patients, including those who are unlikely to benefit from the addition of more HMAs.

Venetoclax Safety Issues
The most common AEs (≥ 20%) observed during the VIALE-A study were gastrointestinal disorders (42.8%), due in large part to diarrhea (13.3%), infection (12.9%), and neutropenia (10.6%). Nausea (5.9%), hyperbilirubinemia (4.7%), and pyrexia (4.7%) were the most common AEs (≥ 20%) observed during the VIALE-C study. He noted that adverse events that were particularly high in the VIALE-A study were febrile neutropenia (42%) and thrombocytopenia (46%). In contrast, in the VIALE-C study, febrile neutropenia (42%) and anemia (28%) were the most common AEs (≥ 20%).

He noted several reasons why the VIALE-C study was underpowered, including the inclusion of patients who had previously received an HMA and the relatively small number of patients enrolled. "It was a very expensive study with a lot of work that went into it," he said. "The reason we have to keep doing studies is because a lot of them are not going to work, and we need to figure out which ones do."

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Table 1. Prevalence of Hematologic AEs Observed With Venetoclax in the VIALE Studies

<table>
<thead>
<tr>
<th>Hematologic AE</th>
<th>VIALE-A (venetoclax plus azacitidine)</th>
<th>VIALE-C (venetoclax plus LDAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46%</td>
<td>45%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Anemia</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21%</td>
<td>21%</td>
</tr>
</tbody>
</table>

AE, adverse event; LDAC, low-dose cytarabine; NR, not reported.
with venetoclax in combination with azacitidine, decitabine, or LDAC in clinical trials were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutro-
penia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyn-
geal pain, and hypotension. In the VIALE studies, the most frequently reported AEs were hematologic events (TABLE 1).\(^1,4\)

Of note, venetoclax has a warning regarding tumor lysis syndrome; however, it appears to be uncommon in patients with AML. “It’s important to watch and to be care-
ful, especially with the first few doses, but it’s much less common than what you would see with chronic lymphocytic leukemia,” Amir Fathi, MD, said.

He noted that his greatest concern with venetoclax is the lack of consistency in how it is used in combination with HMA’s in community practices. “I can’t tell you how many patients we’ve admitted to our ICUs [intensive care units] who have been treated in the community with HMA/venetoclax cycle after cycle after cycle and end up with severe marrow suppression, infections, and bleeding complications,” he said.

Fathi added that although some nuances in treatment will always exist, a more consistent approach is needed.

He said that in his practice, he starts with 4 weeks of venetoclax plus the HMA and then conducts a bone marrow biopsy to assess blast level. “If the marrow is empty, I allow count recovery [by holding venetoclax] and then resume. If it is full of blasts, I go with the second cycle,” he said.

If blast depletion occurs repeatedly, Fathi added, the intensity of treatment should be decreased, noting that he usually reduces treatment to 2 or 3 weeks in such cases.

Additionally, he said clinicians must consider concurrent medications, particularly the azoles [eg, isavuconazole sulfate [Cressemba], voriconazole [Vfend], and posaconazole [Noxfail]]. “You have to reduce the dose...otherwise you’re going to get in trouble with marrow suppression,” he said.

Roboz agreed with Fathi: “Please don’t have on day 60 of venetoclax without a bone marrow biopsy. Please don’t add an antifun-
gal. If you’re going to add it, you’ve got to down the dose. At least certain basic prin-
ciples must be absolutely applied, even if the subtleties of exactly what day you do the marrow and exactly which antifungal can’t be mandated.”

### TARGETING IDH MUTATIONS

Approximately 20% of patients with AML have IDH mutations, with IDHI mutations found in 6% to 16% of patients and IDH2 mutations found in 8% to 19%.\(^4\) These mutations are associated with a poor prognosis.\(^6\) Before treatments targeting IDHI mutations were developed, “we [had] been pummeling [such patients] for decades with lots of different chemotherapy combinations without success,” Roboz said.

The emergence of IDH inhibitors enables clinicians to treat patients with IDHI mutations with a single-agent regimen that provides high response rates and durable remissions, often lasting 6 to 12 months, she said. Based on such findings in the relapsed setting, the IDH inhibitors ivosidenib, a potent IDHI inhibitor, and enasidenib, a potent IDH2 inhibitor, have also been explored as treatments in the frontline setting. Both agents are currently FDA approved for adult patients with relapsed/ refractory AML, with ivosidenib also approved as a first-line treatment.\(^7,4\) Several studies are currently examining these agents in combination treatments, including with venetoclax and azacitidine. An advantage of both agents is that they are taken orally, which may be particularly beneficial for some patients during the ongoing coronavirus disease 2019 (COVID-19) pandemic.

### Ivosidenib

Ivosidenib received FDA approval in May 2019 as a first-line treatment in patients with a susceptible IDHI mutation, as detected by an FDA-approved test, who are not candidates for intensive induction chemotherapy because of age (\(\geq 75\) years) or comorbidities.\(^5\) Approval was based on the open-label, single-arm, multicenter AG120-C-001 study (NCT02074839), which included 28 such patients. Of these patients, 12 (42.9%) achieved CR and CR with partial hematologic recovery (CRh) and 7 of the 17 transfusion-dependent patients (41.2%) achieved transfusion independence lasting at least 8 weeks.\(^8\)

“These are patients who might not actually have been offered anything. They were the patients who are older and may have fallen into the nihilism trap. And yet here they are in a durable remission,” Roboz said.

Adding the HMA azacitidine to ivosidenib has also shown benefit. In a phase 1b/2 study (NCT02677922), the combination resulted in a high rate of clinical response with molecular remissions in patients ineligible for intensive chemotherapy.\(^10\) Investigators are assessing the combination for such patients in the phase 3 AGILE trial (NCT03173248).\(^11\) Participants are being randomly assigned 1:1 to ivosidenib 500 mg daily plus azacitidine 75 mg/m\(^2\) subcutaneously or intravenously for 7 days in 28-day cycles or to matched placebo plus

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<table>
<thead>
<tr>
<th>TABLE 2. Most Common AEs (≥30%), Boxed Warning Associated With Ivosidenib and Enasidenib(^7,8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivosidenib</strong></td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

**Boxed warning:**

**Differentiation syndrome:** Patients treated with ivosidenib or enasidenib have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

AE, adverse event.

*Prescribing information for both ivosidenib and enasidenib contain a boxed warning for differentiation syndrome.
azacitidine. The study is enrolling patients globally; however, enrollment has slowed because of COVID-19, and it is now expected to be completed in 2021.

Further, investigators are conducting a phase 1/2 study (NCT03471260) of ivosidenib in combination with venetoclax with or without concomitant azacitidine in patients with treatment-naïve (n = 5) and relapsed (n = 9) IDH1-mutated AML.

Roboz said venetoclax has demonstrated efficacy in both IDH subgroups, making it an appealing partner for IDH-directed combination therapy. In the study, the composite CR (CR plus CR with incomplete hematologic recovery plus CRh) was 100% in the treatment-naïve cohort and 75% in the relapsed/refractory cohort. After a median follow-up of 3.5 months, the median OS was not reached in treatment-naïve patients and was 9.7 months in the patients with relapsed/refractory disease.

Enasidenib
Erba said that presentations by Courtney D. DiNardo, MD, MSCE, on phase 2 trial data involving azacitidine alone versus azacitidine plus enasidenib were among the most interesting studies at the European Hematology Association and American Society of Clinical Oncology conferences. The study (NCT02677922) included 101 patients with newly diagnosed IDH2-mutated AML who were randomly assigned 2:1 to the azacitidine/enasidenib combination (n = 68) or azacitidine monotherapy (n = 33). Both cohorts had a median OS of 22 months; however, the combination therapy arm had improvements in event-free survival (17.2 months vs 10.8 months), overall response rates (71% vs 42%), median duration of response (24.1 months vs 12.1 months), and complete response rates (53% vs 12%).

Fathi warned about drawing conclusions about the OS data from this study because they are from the phase 2 portion of an open-label phase 1/2 randomized trial and not from a phase 3 randomized trial such as the VIALE studies. He noted this is an important consideration when thinking about combination therapies (ie, venetoclax/HMAs vs IDH inhibitor HMAs). His preference is to use venetoclax/HMA in younger patients and those who can tolerate the combination, reserving the IDH inhibitors as a subsequent treatment option. “However, if I think a patient may tolerate the HMA/IDH inhibitor better, I generally go with that. I like to have options so that I can prolong a patient’s survival with sequential therapy. There are no data, obviously, to guide that, but that’s just been my general approach with these patients,” he said.

After the Peer Exchange, Bristol Myers Squibb, the manufacturer of enasidenib, reported a further development with the drug. Enasidenib plus best supportive care (BSC) was not found to significantly improve OS in patients with IDH2-mutated relapsed/refractory AML in the phase 3 IDHENTIFY trial (NCT02577406), thereby failing to meet the study’s primary end point.

In the study, enasidenib plus BSC was compared with conventional care regimens, including BSC alone, azacitidine plus BSC, LDAC plus BSC, and intermediate-dose cytarabine plus BSC. A full evaluation of the IDHENTIFY data is ongoing and is expected to be presented at a future medical meeting.

IDH INHIBITOR SAFETY
The most common AEs observed with ivosidenib and enasidenib in clinical trials are listed in TABLE 2. The panelists said they do not undertake dose adjustments when they observe hyperbilirubinemia from inhibition of UGT1A1 in patients treated with enasidenib. “It’s a measure of patient adherence,” Mark J. Levis, MD, PhD, said. Roboz agreed and explained that stopping therapy in some cases would be a mistake.

They also noted that QT prolongation has been observed with ivosidenib. Although uncommon, Guillain-Barré syndrome was identified in some of these cases. “In our phase 1 experience, Guillain-Barré [occurred] in 2 of about 250 patients,” Erba said. Levis said he has also seen such a case; thus, clinicians should be aware of this association.

Although their AE profiles are a bit different, a potential AE that both IDH inhibitors share is differentiation syndrome, a potentially life-threatening complication that is noted in a boxed warning in their prescribing information. “If you look at study after study with IDH inhibitors, either as monotherapy or a combination with induction for HMA, you’ll see approximately 12% to 20% of patients getting differentiation syndrome,” Fathi said, noting it is a difficult entity to tease out because it has a vague constellation of symptoms, many of which may be associated with other causes. He explained that common symptoms seen in patients with IDH-associated differentiation syndrome include unexplained fever, respiratory issues, pleural effusions, pericardial effusions, rash, mild azotemia, bone pain, and adenopathy.

Importantly, although clinicians should try to rule out secondary causes of these symptoms, if they cannot do so easily or quickly, they should treat the patients as though they have differentiation syndrome, Fathi explained. “[In such cases], initiation of steroids is important because these conditions can escalate,” he said, recommending dexamethasone 10 mg twice daily for such patients. “Then once patients get better, and they should if it is differentiation syndrome, there should be a tapering down of the dose over time,” he said.

Unlike the differentiation syndrome observed in patients with acute promyelocytic leukemia treated with all-trans retinoic acid, IDH inhibitor-related differentiation syndrome in patients with AML is delayed. “The median time of loss was around 12 weeks. So anywhere between 10 days and 6 months, you can potentially get it. If you stop treatment and resume it later, you can get recurrent episodes of differentiation syndrome,” Fathi said. He concluded by stating that the condition sometimes occurs with other AEs, including leukocytosis, disseminated intravascular coagulation, and tumor lysis syndrome, and that such cases will require additional measures, such as the addition of hydroxyurea in the setting of concurrent leukocytosis.
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