Investigators Prepare for the Next Wave of Immunotherapy Advances
IN A WORLD FILLED WITH COVID-19...

CIN CAN STRIKE AT ANY MOMENT

It's time to take a crucial new look at CIN, the dire consequences of leaving patients unprotected, and how the COVID-19 pandemic is changing guidelines as well as your approach to providing the best standard of care.

TO LEARN MORE, VISIT CINRisk.com

With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer.

Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.1

When your patients are left unprotected, particularly in Cycle 1,2 CIN may lead to life-threatening events, such as fever, infection, and hospitalization3–severely disrupting the predictability of your treatment plan.

These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.4-6

References:
With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.¹

When your patients are left unprotected, particularly in Cycle 1,² CIN may lead to life-threatening events, such as fever, infection, and hospitalization³—severely disrupting the predictability of your treatment plan. These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.⁴⁻⁶

Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 68.
New data has shined a light on the utility of immunotherapies as neoadjuvant and adjuvant treatment options in earlier stages of disease. At the 6th Annual International Congress on Immunotherapies in Cancer® cochair Charu Aggarwal, MD, MPH, will lead discussions contextualizing the practical application of the recent wave of approvals across tumor types.
BETTER IS HOME TO NEW JERSEY’S BEST CANCER CENTER

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

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
Liquid Biopsy Opens Doors for Immunotherapy

IMMUNOTHERAPY HAS STRONG ROOTS as the treatment of choice for several tumor types. As the value of immune checkpoint inhibitors in combination and as single agents continues to expand across malignancies, so too does the need to identify patients for whom the clinical benefit of such agents supersedes that of standard care.

Enter liquid biopsy. These assays, used to identify biomarkers in blood and plasma samples from patients, are useful not only for initial diagnosis, but also when evaluating efficacy of ongoing treatments. Further, liquid biopsies are cheaper, can be obtained quicker, and are less painful for the patient.

Described by her colleagues as a “pioneer” in liquid biopsy, Charu Aggarwal, MD, MPH, notes in the cover story in this issue of OncologyLive®, that “with the explosion of immunotherapy, we can now deliver [agents] safely with a survival benefit for most of our patients. There will always be a subset [of patients who] cannot get immunotherapy, but for the vast majority of our patients, they can, and we can use testing to determine which patients can get immunotherapy alone.”

Aggarwal has been a key investigator into liquid biopsy, specifically in non–small cell lung cancer (NSCLC). Results of a recent study of Aggarwal’s highlighted the association of KRAS variant status and its relation to outcomes for patients treated with immunotherapy alone vs those who received immunotherapy plus chemotherapy. Results did not show a significant survival benefit among those with KRAS-mutant disease; however, the absence of a mutation demonstrated that those treated with chemoimmunotherapy had improved survival, even though it was not statistically significant. The median overall survival in this subgroup was 13.6 vs 19.3 months, respectively (adjusted HR, 1.19; 95% CI, 0.89-1.58; \( P = .06 \)).

Aggarwal will cochair the 6th Annual International Congress on Immunotherapies in Cancer® along with Mario Sznol, MD, on Saturday, December 11, at the InterContinental New York Times Square. The immunotherapy conference, hosted by Physicians’ Education Resource® (PER®), offers an opportunity to engage with the experts who helped define the field. For instance, Aggarwal, Sznol, and Jeffrey Weber, MD, will host a panel on immune-related adverse events during which attendees are invited to bring their own cases for discussion.

The meeting agenda will focus on evaluating the most recent data from clinical trials and implementing practical strategies for the treatment of solid tumors and hematologic malignancies. “What I want the attendees to take out of this conference is practical information on how to apply chemotherapy or immunotherapy in the clinic, in the context of new clinical information and new clinical trials that have been presented at recent meetings,” Aggarwal said. For more information, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCE

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
- Adult patients with metastatic RET-mutant medullary thyroid cancer (MTC) who require system therapy
- Adult patients with metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

**INDICATIONS**

| Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy | Ξ
| Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test | Ξ
| Adult patients with metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) | Ξ

**IMPORTANT SAFETY INFORMATION**

**Interstitial Lung Disease (ILD)/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 (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 aspartate aminotransferase (AST) occurred in 69% of patients, including Grade 3/4 in 5% and increased alanine aminotransferase (ALT) occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 17 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

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

**Tumor Lysis Syndrome (TLS):** Cases of TLS have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

**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.

**Pregnancy:** 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%):** constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. Common Grade 3/4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets and increased alkaline phosphatase.

**Avoid coadministration of GAVRETO with strong CYP3A inhibitors or 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 on adjacent pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch, or call 1-800-FDA-1088.
INDICATIONS AND USAGE

Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
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 on overall response rate and duration of response. Continued approval for this indication is approved under accelerated approval based on on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification on overall response rate and duration of response.

RET-Mutant Medullary Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. 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 on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification on overall response rate and duration of response.

RET Fusion-Positive Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with RET fusion-positive advanced or metastatic thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). 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 on overall response rate and duration of response.

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% 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.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described above:

- Interstitial Lung Disease/Pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic Events
- Tumor Lysis Syndrome
- 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 tumors, including with RET fusion-positive NSCLC (n=220), and RET-altered thyroid cancer (n=138), 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.

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

**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. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year.

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 which occurred in > 1 patient included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

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

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

**Adverse Reactions (≥15%) in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue1</td>
<td>35</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
</tr>
<tr>
<td>Edema²</td>
<td>20</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea³</td>
<td>24</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>16</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain4</td>
<td>32</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension²</td>
<td>28</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal</strong></td>
<td></td>
</tr>
<tr>
<td>Cough4</td>
<td>23</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia²</td>
<td>17</td>
</tr>
</tbody>
</table>

**Select Laboratory Abnormalities (≥20%) Worsening from Baseline in RET Fusion-Positive NSCLC 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>74</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>49</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>39</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>36</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>35</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>29</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>61</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>58</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>56</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>27</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 216 to 218 patients.

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

**RET-altered Thyroid Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diabetes, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reactions occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included fatigue, pneumonia, and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting,
pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue, and thrombocytopenia.

### Adverse Reactions (≥ 15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain¹</td>
<td>42</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
</tr>
<tr>
<td>Diarrhea²</td>
<td>34</td>
</tr>
<tr>
<td>Abdominal Pain¹</td>
<td>17</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>17</td>
</tr>
<tr>
<td>Stomatitis⁴</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue⁵</td>
<td>38</td>
</tr>
<tr>
<td>Edema⁶</td>
<td>29</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache¹</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral Neuropathy⁴</td>
<td>20</td>
</tr>
<tr>
<td>Dizziness⁵</td>
<td>19</td>
</tr>
<tr>
<td>Dysgeusia⁶</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough¹¹</td>
<td>27</td>
</tr>
<tr>
<td>Dyspnea¹²</td>
<td>22</td>
</tr>
<tr>
<td>Skin and Subcutaneous</td>
<td></td>
</tr>
<tr>
<td>Rash¹³</td>
<td>24</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>15</td>
</tr>
</tbody>
</table>

¹ Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
² Diarrhea includes colitis, diarrhea
³ Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
⁴ Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
⁵ Fatigue includes asthenia, fatigue
⁶ Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
⁷ Headache includes headache, migraine
⁸ Peripheral neuropathy includes dysaesthesia, hypeaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
⁹ Dizziness includes dizziness, dizziness postural, vertigo
¹⁰ Dysgeusia includes ageusia, dysgeusia
¹¹ Cough includes cough, productive cough, upper-airway cough syndrome
¹² Dyspnea includes dyspnea, dyspnea exertional
¹³ Rash includes dermatitis, dermatitis acnéiform, eczema, palmar-plantar, erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular

* Only includes a Grade 3 adverse reaction

Clinically relevant adverse reactions in <15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

### Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>70</td>
</tr>
<tr>
<td>Increased AST</td>
<td>69</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>43</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>41</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>28</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>28</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>24</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>22*</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>67</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>63</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>59</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>31</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 135 to 138 patients.

Clinically relevant laboratory abnormalities in patients who received GAVRETO included increased phosphate (40%).

### 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 of GAVRETO with strong CYP3A inducers cannot be avoided, increase the GAVRETO dose.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

**Risk Summary**

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated 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.
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 doses levels ≥20 mg/kg (approximately 1.8 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 0.6 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.

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 been established in pediatric patients aged 12 years and older for RET-mutant MTC and RET-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of RET-mutant MTC and RET-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The safety and effectiveness of GAVRETO have not been established in pediatric patients with RET fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET-mutant MTC or RET-fusion thyroid cancer.

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

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

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

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

Manufactured for: Blueprint Medicines Corporation, Cambridge, MA 02139, USA
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For more information, go to www.GAVRETO.com or call 1-888-258-7768.
The Challenging Future of the FDA in the Cancer Arena

by MAURIE MARKMAN, MD

It is difficult to overstate the current challenges facing the FDA. From decisions regarding the use of COVID-19 vaccines in children to the polarization among government officials and the scientific community associated with approval of COVID-19 booster shots, our nation’s drug regulatory agency appears to increasingly be a topic of discussion in the mainstream and social media. Unfortunately, much of this attention, and the headlines generated, are not favorable to the mission of this critical federal scientific public health agency.

For example, consider the still poorly understood decision by the FDA to approve the Alzheimer’s drug, aducanumab-avwa (Aduhelm). The decision was made despite the overwhelming disapproval of the agency’s own advisory committee, highlighting a concerning degree of dysfunction within what is arguably one of most vitally important government organizations. 1

And although likely not high on the list of priorities, several issues reported in the scientific press await review, careful consideration, and possible action from the FDA. These include the potential evidence of scientific misconduct according to a self-reported survey from Dutch scientists that if widespread throughout the scientific community has the realistic potential to influence reports of pharmaceutical drug efficacy and/or safety; evidence of inadequate protection of research subjects by investigators and institutional review boards in federally funded research projects such as a recent study of vitamin D supplementation in asthmatic children; and potentially problematic editorials related to cancer pharmaceutical agents, which are regulated by the FDA, among individuals with a financial relationship with industry. 4

The FDA has suffered from what some might appropriately argue is a stunningly ineffective public communication strategy with an apparent inability to clearly explain both the safety of established vaccines in the United States and provide clarity on the extensive multistep regulatory process required before any vaccine product is approved for noninvestigative use.

The example often stated of the rushed approval of the COVID-19 mRNA–based products is an important case to highlight. mRNA-based drugs—not COVID-19 vaccines—have been under active clinical investigation and FDA oversight for almost 10 years in the oncology arena and more than 3 years in the management of infectious diseases prior to the COVID-19 pandemic. 5 Therefore, the FDA had extensive experience with the potential safety and manufacturing issues associated with mRNA COVID-19 vaccines before clinical trials in this area were initiated. One might inquire why it has been so difficult for the FDA to clearly communicate these and other objective facts and observations regarding the development of these remarkably safe, effective, and life-saving vaccines?

Outside of communications related to COVID-19, it is not difficult to create a list of items requiring meaningful consideration from the agency.

For example, evolving issues include the future approval processes and potential restrictions of use of antineoplastic pharmaceutical agents. To eliminate the risk of bias in the review of imaging studies, most commonly CT scans, defining the time to disease progression for women on ovarian cancer trials, the FDA has routinely mandated independent blinded radiology review vs accepting the opinion of the local-site radiologist as to when the cancer has progressed. 6 However, strong evidence exists that independent radiographic review results in outcomes very similar to that of the treating team. 6 Based on these data, how much longer will this time-intensive and extremely costly third-party review effort be required?

Recent studies have demonstrated the impressive effect of PARP inhibitors in both the therapeutic and maintenance settings in the treatment of ovarian cancer and other malignancies including breast, prostate, pancreatic cancers. However, evolving and not terribly surprising...
data have suggested the development of myelodysplastic syndrome and acute leukemia in a small, but likely not rare, group of patients receiving one of this class of drugs.\(^7,8\) How should the FDA respond to this information in terms of advising clinicians regarding the overall risk and/or strategies to mitigate that risk?

Finally, there is the issue of establishing appropriate control arms in a phase 3 trial during which a previously approved strategy in the clinical setting is being tested. What is the FDA’s guidance for determining an appropriate comparator arm in a scenario where clinicians may not routinely treat patients with the specific approved regimen?

Consider the FDA’s approval of bevacizumab (Avastin) plus one of 3 cytotoxic chemotherapeutic agents in platinum-resistant ovarian cancer, based on data from the landmark AURELIA trial (NCT00976911).\(^9\) Should a novel drug strategy in platinum-resistant ovarian cancer be required to demonstrate superiority to chemotherapy alone, such as in the FORWARD 1 study (NCT02631876),\(^10\) or should chemotherapy plus bevacizumab, the superior study arm in the AURELIA trial, be used? If a direct comparison to the chemotherapy plus bevacizumab regimen in AURELIA is not mandated, one might suggest that an explanation from the FDA is required because in the absence of such data, it is quite uncertain how clinicians will objectively determine the more effective regimen for their patients with platinum-resistant disease.

Although the proceeding examples highlight the ongoing regulatory concerns that demand attention of the FDA in the gynecologic cancer arena because of the specific clinical and research interest of the commentator, these issues extend to other areas of oncology and put into perspective the scope of the areas where FDA holds influence.

**REFERENCES**

2. de Vrieze J. Large survey finds questionable research practices are common. *Science*. 2021;373(6552):265. doi:10.1126/science.373.6552.265
Zanubrutinib Moves Forward for Relapsed or Refractory MZL

The FDA has granted accelerated approval to zanubrutinib (Brukinsa) for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 anti–CD20-based regimen.

The regulatory decision is based on efficacy data yielded from 2 trials: the phase 2 MAGNOLIA trial (GBG-3111-214; NCT03846427), which evaluated 66 patients with MZL who received at least 1 prior anti–CD20-based regimen, and the phase 1/2 BGB-311-AU-003 trial (NCT02343120), which included 20 patients with previously treated MZL.

Results from the MAGNOLIA trial indicated that the agent elicited a CT-based overall response rate (ORR) of 56% (95% CI, 43%-68%) with a 20% complete response (CR) rate and a 36% partial response (PR) rate. In the BGB-311-AU-003 trial, zanubrutinib demonstrated a CT-based ORR of 80% (95% CI, 56%-94%), which included a CR rate of 20% and a PR rate of 60%.

The median duration of response was not estimable for both studies at a median follow-up of 8.9 months and 31.4 months, respectively. Eighty-five percent (95% CI, 67%-93%) and 72% (95% CI, 40%-88%) of patients were still in remission at 12 months in the MAGNOLIA and BGB-311-AU-003 studies, respectively.

Mobocertinib Approval Opens Door for Patients With NSCLC With EGFR Exon 20 Insertion Mutations

The FDA has granted accelerated approval to mobocertinib (Exkivity) for the treatment of adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

Support of the agent was based on data collected from a phase 1/2 trial (NCT02716116). Per a blinded independent central review, results showed that mobocertinib elicited a 28% overall response rate (95% CI, 20%-37%) among the 114 evaluable patients. The median duration of response was 17.5 months (95% CI, 7.4-20.3), with 59% of these patients having observed responses lasting at least 6 months.

Additionally, the regulatory agency gave the green light to Thermo Fisher Scientific’s Oncomine Dx Target Test as a next-generation sequencing companion diagnostic device for the agent to identify patients with NSCLC harboring EGFR exon 20 insertion mutations, includes a box warning for ocular toxicity.

Cabozantinib Gets Go-Ahead for Differentiated Thyroid Cancer

The FDA has approved cabozantinib (Cabometyx) for the treatment of adult and pediatric patients 12 years and older with locally advanced or metastatic differentiated thyroid cancer that has progressed after prior VEGF-targeted therapy and who are ineligible or refractory to radioactive iodine. The approval is maintained by findings from the phase 3 COSMIC-311 trial (NCT03690388), in which cabozantinib proved to significantly reduce the risk of disease progression or death vs placebo.

In an updated analysis, the median progression-free survival was 11 months (95% CI, 7.4-13.8) in the intention-to-treat arm compared with 1.9 months (95% CI, 1.9-3.7) in the placebo arm (HR, 0.22; 95% CI, 0.15-0.31). The overall response rate was 18% (95% CI, 10%-29%) among the 170 patients in the cabozantinib arm and 0% (95% CI, 0%-11%) among the 88 patients in the placebo arm, which investors noted was not statistically significant.

Cabozantinib gets go-ahead for differentiated thyroid cancer.

Ruxolitinib Approval Contributes to Treatment Advances in Chronic GVHD

Ruxolitinib (Jakafi) outperformed best available therapy (BAT) and received approval from the FDA for the treatment of adult and pediatric patients 12 years and older with chronic graft-vs-host-disease (GVHD) following failure of 1 or 2 lines of systemic therapy. Efficacy was supported in the phase 3 REACH3 trial (NCT03112603), which included 101 patients who had received no more than 2 prior systemic therapy regimens in the recurrent or metastatic setting, including at least 1 prior platinum-based chemotherapy regimen. Sixty-nine percent of patients had received bevacizumab (Avastin) as part of prior systemic therapy.

The data indicated a 24% objective response rate (95% CI, 15.9%-33.3%), which comprised a 7% complete response rate and a 17% partial response rate. The median duration of response was 8.3 months (95% CI, 4.2-not reached). The median time to response with tisotumab vedotin was 1.4 months (range, 1.1-5.1), and activity was noted within the first 2 treatment cycles. The product labeling includes a box warning for ocular toxicity.

The median duration of response—calculated from first response to progression of disease or death—was 5.4 months (95% CI, 4.2-6.7) for the ruxolitinib and BAT arms, respectively. Response rates were 8% vs 5% and the partial response rates were 62% vs 52% in the ruxolitinib and BAT arms, respectively.

Tisotumab Vedotin Moves Ahead for Recurrent or Metastatic Cervical Cancer

Tisotumab vedotin-tftv (Tivdak), a tissue factor-directed antibody and microtubule inhibitor, has been granted accelerated approval by the FDA for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemothera.
Nearly 5 years

What could this data mean for your patients?

Find out at KISQALI-hcp.com
Cemiplimab Expands Treatment Portfolio for Patients With Basal Cell Carcinoma

by KYLE DOHERTY and CAROLINE SEYMOUR

PATIENTS WITH ADVANCED BASAL cell carcinoma (BCC), both metastatic and locally advanced, have a new treatment option with the approval of cemiplimab-rwlc (Libtayo). On February 9, the FDA granted regular approval to cemiplimab for patients with locally advanced BCC previously treated with a hedgehog inhibitor (HHI) or for whom a HHI is not appropriate. An accelerated approval was granted for the indication that includes patients with metastatic disease previously treated with a HHI or for whom a HHI is not appropriate.1

The approvals were based on results from the phase 2 EMPOWER-BCC 1 trial (NCT03132636), which showed the agent elicited an overall response rate (ORR) of 21% (95% CI, 8%-41%) in patients with metastatic BCC (n = 28) and an ORR of 29% (95% CI, 19%-40%) in patients with locally advanced BCC (n = 84). The median duration of response was not reached in either group.2 Among the responders in the locally advanced group, 79% maintained a response at 6 months; all responders in the metastatic group maintained a response at 6 months.

In terms of safety, the agent was well tolerated, and the most common adverse events of any grade in the 132-patient safety population were fatigue (49%), musculoskeletal pain (33%), and diarrhea (29%). Common grade 3/4 adverse events included fatigue (3.8%), decreased appetite, and musculoskeletal pain (1.5% each).2

Alexander J. Stratigos, MD, PhD, a professor of dermatology and venereology in the Department of Dermatology at the University of Athens Medical School in Greece, discussed the effect cemiplimab will have on the treatment landscape of patients with advanced BCC in an interview with OncologyLive®.

Q Please elaborate on the data reported from the phase 2 study.

This was an open-label, multicenter, nonrandomized phase 2 trial that included patients with unresectable locally advanced BCC, as well as patients with metastatic BCC, either with nodal metastasis or distant metastatic disease. These patients were treated previously treated with HHI therapy. This study was the largest prospective clinical trial among this patient population and included 112 patients in the efficacy analysis, with 84 patients with locally advanced BCC and 28 patients with metastatic BCC.

In advanced BCC, tumors were shown to be responsive to cemiplimab in both patients with metastatic and locally advanced disease. The confirmed ORR was 21% in patients with metastatic disease and 29% in patients with locally advanced disease. The most common adverse reactions reported in the trial in at least 15% of patients were fatigue in 49% of patients, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection. [These are] the usual safety issues we see with other anti–PD-1 therapies.

Q What is significant about the approval of cemiplimab for patients with advanced BCC?

There have previously been limited treatment options for patients with advanced BCC following either intolerance or progression with HHI therapy. With the FDA approval of cemiplimab, these patients now have a new immunotherapy option for the treatment of advanced BCC after HHI therapy. It’s very encouraging that the trial [results] showed meaningful clinical responses and also durable responses with cemiplimab.

This is the first immunotherapy treatment for patients with advanced BCC. It’s also the first treatment to show a clinical benefit in patients with advanced BCC, either locally advanced or metastatic disease following a HHI therapy in a pivotal trial.

Cemiplimab is a fully humanized monoclonal antibody that targets the immune checkpoint receptor PD-1, which is located on T cells. Like other anti–PD-1 therapies, cemiplimab binds to PD-1 and has been shown to block cancers from suppressing T-cell activation.

Q Based on the data seen in pretreated patients so far, is there rationale to suggest that cemiplimab may potentially move into the frontline setting at some point, whether alone or in combination with another agent?

The data have been certainly very encouraging in the second-line setting, and the option of using this immunotherapy in this first-line setting is also quite encouraging. This is something that we should consider either as a monotherapy or, as you suggested, [in] combination with other therapies.

Q Is there any other element of the approval or ongoing or planned research with cemiplimab that investigators should be aware of?

The FDA granted an accelerated approval for the metastatic disease indication for cemiplimab. [Based on this], cemiplimab is continuing to be investigated in this patient group as part of the ongoing phase 2 EMPOWER-BCC 1 study.

[Additionally,] there is research focused on biomarkers as predictors of response to immunotherapy in this particular patient setting. In my opinion, [this approval] is significant news for patients with advanced BCC, and it expands the scope of immunotherapy in this patient setting. We’re very much encouraged by the fact that there is now a treatment showing clinical benefit in patients with advanced BCC following HHI therapy.

REFERENCES


EMPOWER-BCC 1 (NCT03132636) is an ongoing, open-label, multicenter, nonrandomized phase 2 trial in patients with advanced BCC (laBCC or mBCC) who progressed on HHI therapy, had no objective response after 9 months on HHI therapy, or were intolerant of prior HHI therapy.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
<th>70 (42-89)</th>
<th>65.5 (38-90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>laBCC cohort (n = 84)</td>
<td>79.2%</td>
<td>100%</td>
</tr>
<tr>
<td>mBCC cohort (n = 28)</td>
<td>29% (19%-40%)</td>
<td>21% (8%-41%)</td>
</tr>
<tr>
<td>Prior treatment (%)</td>
<td>83%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Prior treatment includes ≥ 1 prior cancer-related surgery and/or prior radiotherapy.

MBC cohort only

- Distant metastases: 14%
- Nodal disease: 54%
- Both distant and nodal disease: 32%

Primary basal cell carcinoma site

- laBCC cohort only
  - Head and neck: 89%
  - Trunk: 2%
  - Arm or leg: 8%

<table>
<thead>
<tr>
<th>Commonly reported adverse effects in the EMPOWER-BCC 1 trial</th>
</tr>
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<tbody>
<tr>
<td>Adverse effect</td>
</tr>
<tr>
<td>----------------</td>
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<tr>
<td></td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Musculoskeletal pain</td>
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<td>Diarrhea</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Pruritus</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<tr>
<td>Decreased appetite</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Constipation</td>
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<tr>
<td>Dyspnea</td>
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</tbody>
</table>

REFERENCE

INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:

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

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

IMPORTANT SAFETY INFORMATION

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

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

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

### Treatment-naive Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>DoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>fusion-positive NSCLC</td>
<td>85% (95% CI: 70, 94)</td>
<td>Median DoR not yet reached (95% CI: 12, NE); median follow-up: 7.4 months</td>
</tr>
</tbody>
</table>

### Previously Treated Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>DoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>fusion-positive NSCLC</td>
<td>64% (95% CI: 54, 73)</td>
<td>Median DoR was 17.5 months (95% CI: 12, NE); median follow-up: 12.1 months</td>
</tr>
</tbody>
</table>

### Responses in Intracranial Lesions

- **10 of 11** previously treated patients with measurable brain metastases received retavmo.
- CNS DoR was ≥6 months in all responders with measurable brain metastases.
- No patients received radiation therapy to the brain within 2 months prior to study entry.

### Find RET. Find results on Retevmo.com.

**Trial Design** The phase II/III, multicohort, open-label, single-arm, multicenter LIBRETTO-001 trial evaluated the efficacy of Retevmo in a population of 702 patients with metastatic RET fusion-positive NSCLC (n=332), advanced or metastatic RET fusion-positive thyroid cancer (non-MTC) (n=38), advanced or metastatic RET-mutant MTC (n=306), and certain other advanced solid tumors with RET alterations (n=26). The study enrolled the following cohorts: systemic therapy-naive patients (n=59) and previously treated (n=105) patients who had progressed on platinum-based chemotherapy with metastatic RET fusion-positive NSCLC, systemic therapy-naive (n=8) and previously treated (n=19) patients with advanced or metastatic RET fusion-positive thyroid cancer (non-MTC), and treatment-naive (n=88) and previously treated (n=55) patients with advanced or metastatic RET-mutant MTC. Major efficacy outcomes were ORR and DoR. In phase II, the dose for Retevmo was 160 mg PO BID. ORR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v1.1. All results reviewed by an IRC.

### Adverse Reactions and Laboratory Abnormalities

- The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypophosphatemia, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.
- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction in ≥2% of patients was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥1% patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).
- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hyperglycemia, diarrhea, pyrexia, and QT prolongation.
- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.
Important Safety Information for RETEVMO® (selpercatinib 40 mg, 80 mg capsules) (Cont’d)

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

Serious, including fatal, hemorrhagic events can occur with Retevmo. Grade 3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminists. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

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

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

Severe adverse reactions (Grade 3–4) occurring in >15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspepsia (2.3%), fatigue (2%), abdominal pain (1.5%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

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

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

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades; Grade 3–4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2%), and decreased glucose (22%; 0.7%).

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

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

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

Concomitant use of Retevmo with CYP2CB and CYP3A substrates increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2CB and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2CB and CYP3A substrates provided in their approved product labeling.

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

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

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

SE HCP ISAI_25AUG2020

Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.

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

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

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS
Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 8%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. If ALT or AST increases >5 times ULN or ALT >3 times ULN, reduce dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hepatotoxicity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hepatotoxicity.

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

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

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

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

RETEVMO is an inhibitor of RET and VEGF signaling.

RETEVMO can cause QT interval prolongation. A single 600 mg dose of RETEVMO caused a mean QT prolongation of 112 ms and a QTc prolongation of 58 ms.

Impaired wound healing may occur in patients with severe or life-threatening hemmorhage.

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

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity.

RETEVIMO™ capsules, for oral use

Table 1 summarizes the adverse reactions in LIBRETTO-001.

<table>
<thead>
<tr>
<th>Adverse Reaction (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001</th>
<th>RETEVMO (n=702)</th>
<th>RETEVIMO™ (selpercatinib) capsules, for oral use</th>
<th>SE HCP BS 08MAY2020</th>
</tr>
</thead>
</table>

ADVERSE REACTIONS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
<td>18</td>
</tr>
</tbody>
</table>

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

Initial U.S. Approval: 2020

RETEVIMO™ (selpercatinib) capsules, for oral use

Initial U.S. Approval: 2020

RETEVIMO™ (selpercatinib) capsules, for oral use

Initial U.S. Approval: 2020
Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
<th>Grades 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
<td>1.9%</td>
<td></td>
</tr>
</tbody>
</table>

1. Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence.
2. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.
3. Fatigue includes fatigue, asthenia, malaise.
4. Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling face, eye swelling, peripheral swelling.
5. Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.
6. Headache includes headache, sinus headache, tension headache.
7. Includes cough, productive cough.
8. Includes dyspnea, dyspnea exertional, dyspnea at rest.
9. Hemorrhage includes epistaxis, hematuria, hemoptysis, cutaneous or mucosal hemorrhage, vaginal hemorrhage, ecchymosis, hema
techesia, petechiae, traumatic hematomas, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, spontaneous hematoma, abdominal wall hematoma, angina umbilis hemorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic anemia, intrabdominal hemorrhage, lower gastrointestinal hemorrhage, menorrhagia, mouth hemorrhage, occult blood positive, pelvic hematoma, perihepatic hematoma, pharyngeal hemorrhage, pulmonary contusion, purpura, retropertioneal hematoma, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hematoma.

Only includes a grade 3 adverse reaction.

Clinically relevant adverse reactions in ≥15% of patients who received RETEVMO include hypothyroidism (9%).

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO†</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

† Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

Increased Creatinine

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

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

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

Strong and Moderate CYP3A Inhibitors

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

Strong and Moderate CYP3A Inducers

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

Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

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

Drugs that Prolong QT Interval

RETREVMO is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Rats in both the 4- and 13-week toxicology studies had pregnancy losses at maternal exposures less than or equal to the human exposure at the clinical dose. Minipigs also showed signs of minimal to marked increases in fertility at the 160 mg twice daily clinical dose. Rats and minipigs showed increased fetal body weight and malformations (2-3 times the human exposure at the clinical dose) that persisted during the recovery period.

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

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had low levels of early resorptions with only 3 viable fetuses across the 2 litters. All 4 viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

Lactation

Risk Summary

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

RETEVIMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08MM2020

RETEVIMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08MM2020
Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

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

Pediatric Use

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

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

Animal Toxicity Data

In 4-week general toxicology studies in rats, animals showed signs of phsyseal hypertrophy and tooth dysplasia at doses resulting in exposures 3 approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in phsyseal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had increased adverse reactions. If coadministration cannot be avoided, follow recommendations for other indications.

Efffects of Other Drugs on RETEVIMO

In healthy subjects administered RETEVIMO 160 mg orally twice daily, serum creatinine increased 23% and creatinine clearance decreased 24%. There were minimal changes in the other laboratory tests.

In females of reproductive potential prior to initiating RETEVIMO.

Additional information can be found at www.retevmo.com.
Tisotumab Vedotin Displays Efficacy, Tolerability in Cervical Cancer

by KYLE DOHERTY

THE ACCELERATED APPROVAL OF the tissue factor-directed antibody and microtubule inhibitor tisotumab vedotin-tftv (Tivdak) bolsters the treatment portfolio for patients with recurrent metastatic cervical cancer. The FDA granted the approval to tisotumab vedotin on September 20, 2021, specifically for patients in this population who have disease progression on or after chemotherapy.¹

The approval was based on results from the phase 2 innovaTv 204 trial (NCT03438396), which showed that tisotumab vedotin elicited an overall response rate (ORR) of 24% (95% CI, 15.9%-33.3%), including a 7% complete response rate, among 101 treated patients. The median duration of response was 8.3 months (95% CI, 4.2-not reached).²

In an interview with OncologyLive® Robert L. Coleman, MD, chief scientific officer of The US Oncology Network in The Woodlands, Texas, discussed the need to add new agents to the treatment portfolio of recurrent or metastatic cervical cancer and how the approval of tisotumab vedotin may help to fill this void.

Q What are the clinical implications of the FDA approval of tisotumab vedotin in cervical cancer?

This new agent adds to our armamentarium for patients with recurrent metastatic cervical cancer. That’s the bottom line. We have very few effective options. I include immunotherapy in that statement because the vast majority of patients with cervical cancer don’t benefit from immunotherapy. There is certainly a cohort of patients who do remarkably well. We have seen that [immunotherapy is] better than standard chemotherapy in a recent randomized phase 3 trial [KEYNOTE-826, NCT03635567], but that does not close the book. The need for effective therapies, ones that act rapidly, is desperately present in our day-to-day care of patients with advanced metastatic cervical cancer.

The clinical rationale was [primarily] based on the need for effective therapy in patients with recurrent disease post chemotherapy, but also [on the need] to explore a new class of agent. This [agent] is an antibody-drug conjugate that takes advantage of the near-universal expression of tissue factor, which is seen across many solid tumors but is especially high in patients with cervical cancer, [and presents an] opportunity to take advantage of a biological expression of a target and incorporate a targeted smart bomb, so to speak, with chemotherapy that is effective on the cells in the microenvironment.

Q What are the key data points from the innovaTv 204 study you wish to highlight?

The headline that catches individual’s attention is that we have a relatively high response rate. The response rate is in the mid-20s, [which is] usually considered an area that would represent a real clinical advance. That’s why this was submitted under the accelerated approval program. We felt that this was substantially better than our experience with second-line chemotherapy agents in this setting.

The ORR of 24% was felt to be remarkable in this 101-patient trial. The other component of this that sometimes gets lost is that when we treat patients in the clinic, we will make decisions of continuing therapy in the presence of nonprogression. For instance, if a patient comes in who has had a stability in their tumor that we’ve been able to document by exam or by CT scan and symptoms have not accelerated, our strategy at that point is not to change [treatment].

If you look at the proportion of patients for which their best response was progression, it was a really low number. This translates into clinical benefit, which captures the stable disease rate along with all responses. That’s what is meaningful in the clinic. Then, for those patients who respond, the duration of response being more than 9 months or so is substantially meaningful, especially since our life expectancy for this patient population can be quite muted.

Of course, we must balance [these advantages] against the toxicity that was observed.

What are the toxicities clinicians need to be aware of?

The toxicity that we saw with this treatment was not dissimilar to what we see with chemotherapy, although there were a few notable differences. Common adverse effects that we see with chemotherapy in this setting are things such as asthenia and fatigue, bone marrow suppression, alopecia—various adverse effects that we can see with any kind of cytotoxic agent.

The unique toxicities that we saw with [tisotumab vedotin] were ophthalmologic toxicities. Conjunctivitis and neurotoxicity observed with this class of agent are not dissimilar from other antibody-drug conjugates in the literature.

We were also very concerned early on about bleeding during the phase 1 and phase 2 expansion trial because tissue factor is an element that’s present in the clotting cascade. Our concern was that if we were interrupting this process, we were potentially increasing bleeding events. We were happy to see that that wasn’t the case, and we did monitor it very carefully. So, it would be considered a special interest adverse effect.

Fortunately, most of the bleeding events that we saw were epistaxis and others that we’ve seen with [agents such as] bevacizumab [Avastin]. Most of the bleeding that we saw was grade 1 and most of it was resolvable in a short period of time. Overall, we were reassured, but it doesn’t [change] the fact that the optimal logical component of this needs to be addressed. It’s a unique toxicity that, if investigators have not had experience with it, it certainly would be one that they need to pay attention to when they administer the drug.

What does the future hold for tisotumab vedotin?

The agent was brought into the clinical domain under accelerated approval, which means there needs to be a confirmatory trial. That trial has already launched [innovaTv 301, NCT04697628]. [Tisotumab vedotin has] been matched with several different compounds, not only chemotherapy, but also other antiangiogenic agents and immunotherapies that are being investigated to see what might fit best and where in the clinical domain.

[Additionally, we would like to] see it in an earlier line of therapy where we would have an opportunity to provide benefit to more patients in a broader spectrum. It would be logical to assume that an effective second-line agent or third-line agent could be moved up into earlier lines of therapy, where more patients would have access.
PIVOTAL CLINICAL TRIAL

innovaTV 204 (NCT03438396) was an open-label, multicenter, single-arm trial of tisotumab vedotin in adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

BASELINE PATIENT CHARACTERISTICS

Median age, years (range)

50 (31-78)

N = 101

Histology

- Squamous cell carcinoma 68%
- Adenocarcinoma 27%
- Adenosquamous 5%

ECOG performance status

- 0: 58%
- 1: 42%

Prior lines of systemic therapy

- 1: 70%
- 2: 30%

Efficacy results in the innovaTV 204 Trial

Outcome

Tisotumab vedotin (N = 101)

ORR (95% CI) 24% (15.9%–33.3%)

CR 7%

PR 17%

Median DOR, months (95% CI) 8.3 (4.2–NR)

CR, complete response; DOR, duration of response; ORR, overall response rate; NR, not reached; PR, partial response.

WARNINGs AND PRECAUTIONS

- Peripheral neuropathy
- Hemorrhage
- Pneumonitis
- Embryo-fetal toxicity
- Ocular toxicity: Tisotumab vedotin can cause changes in the corneal epithelium and conjunctiva that result in changes in vision, including severe vision loss, and corneal ulceration.
  - Conduct ophthalmic exams including visual acuity and slit lamp exam at baseline, prior to each dose, and as clinically indicated.
  - Adhere to premedication instructions, including topical corticosteroid and vasoconstrictor eye drops, and required eye care before, during, and after infusion.
  - These include the use of cooling eye packs during infusion and topical lubricating eye drops for the duration of therapy and 30 days following treatment.
  - If severe symptoms occur, withhold treatment until improvement and resume, reduce the dose, or permanently discontinue tisotumab vedotin, based on severity.

COMMONLY REPORTED ADVERSE EFFECTS THE innovaTV 204 TRIAL

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Tisotumab vedotin (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>39%</td>
</tr>
<tr>
<td>Nausea</td>
<td>41%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>39%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>39%</td>
</tr>
<tr>
<td>Conjunctival adverse reaction</td>
<td>37%</td>
</tr>
<tr>
<td>Dry eye</td>
<td>29%</td>
</tr>
</tbody>
</table>

*Bevacizumab plus chemotherapy doublet in the first-line setting*
*Cisplatin plus radiotherapy*
*Bevacizumab as part of any prior systemic therapy*

REFERENCE

A selection of exclusive articles and videos available on OncLive.com and other MJH Life Sciences™ websites.
GANDARA ON INCORPORATING MRD TESTING INTO LUNG CANCER PRACTICE

David R. Gandara, MD, says that results of large randomized clinical trials will play a role in the incorporation of minimal residual disease (MRD) testing as a standard of care in clinical practice for patients with lung cancer. Gandara highlights the potential of results from the phase 3 MERMAID-1 (NCT04385368) and MERMAID-2 trials (NCT04642469), which are evaluating MRD testing in patients with stage II/III non–small cell lung cancer to help aid the transition.

WATCH: bit.ly/3u4Ho5N

O’MALLEY ON BALSTILIMAB AND ZALIFRELIMAB IN RECURRENT/METASTATIC CERVICAL CANCER

Future efforts to unpack the efficacy of dual checkpoint blockade in patients with recurrent/metastatic cervical cancer should focus on improving response rates in particular for patients who have PD-L1–negative disease, according to David M. O’Malley, MD. Ongoing trials, such as RaPIDS (NCT03894215), a phase 2 trial evaluating the use of single-agent balstilimab vs the combination of balstilimab plus zalifrelimab, look to add to the growing pool of data.

WATCH: bit.ly/3ux8cMh

JANKU ON THE EFFICACY OF RIPRETINIB IN KIT-MUTATED MELANOMA

Filip Janku, MD, PhD, unpacks the results of a phase 1 study (NCT02571036) of ripretinib (Qinlock), a broad-spectrum KIT and PDGFRA inhibitor, in patients with KIT-mutated or KIT-amplified melanoma. The data demonstrated a higher efficacy than what has previously been reported. Specifically, 1 complete response and 5 partial responses were observed, which translated to an overall response rate of approximately 23% among 26 patients in the intention-to-treat population, Janku explained.

WATCH: bit.ly/2ZchJMT

RAPID READOUTS RESULTS FROM THE PHASE 3 VISION STUDY

A. Oliver Sartor, MD, offers his perspective on data from the phase 3 VISION trial (NCT03511664) that were presented at the 2021 American Society of Clinical Oncology Annual Meeting. Investigators reported that 177Lu-PSMA-617 in addition to standard of care proved to be a well-tolerated regimen that improved radiographic progression-free survival and prolonged overall survival compared with standard of care alone in patients with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer.

WATCH: bit.ly/3nZ6MZm

NOTABLE QUOTABLES

“It is a very exciting time in ovarian cancer. I am thrilled that there is so much investment and development of novel agents and continue [enhancement of] the strategies we have currently, such as PARP inhibitors, checkpoint inhibitors, and bevacizumab [Avastin].”

—Ritu Salani, MD, MBA
University of California, Los Angeles

“The challenge that remains is, are we doing a good enough job at managing [upper gastrointestinal cancer] and curing patients in the end? The short answer is no. This is just the beginning, and the best is yet to come.”

—Yelena Y. Janjigian, MD
Memorial Sloan Kettering Cancer Center
POWERSFUL EFFICACY,
PROVEN TOLERABILITY.

Extend patient survival with
NUBEQA (darolutamide)
in non-metastatic castration-resistant prostate cancer

Focus on both Survival AND Tolerability with NUBEQA

INDICATION
NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

IMPORTANT SAFETY INFORMATION

Embryo-Fetal Toxicity: Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions
Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%) and rash (3% vs 1%).

Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

Drug Interactions
Effect of Other Drugs on NUBEQA – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

Please see the following pages for brief summary of full Prescribing Information.
Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter, phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, 99mTc bone scan by BICR, unacceptable toxicity, or withdrawal. The final analysis of OS and time to initiation of cytotoxic chemotherapy was event-driven and conducted after 254 OS events had occurred and 14 months after MFS analysis.1,2

1In patients treated with NUBEQA + ADT, the most frequent adverse reactions requiring dose reduction included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%); the most frequent adverse reactions requiring dose interruption included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).
2The most frequent adverse reactions requiring permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%).
3All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased AST (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.
4The NUBEQA Free Trial Program provides 1 month’s supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions and to enroll patients, please call Access Services by Bayer at 1-800-288-8374 or visit NUBEQAhcp.com.

PSA=prostate-specific antigen; ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; NE=not estimable; GnRH=gonadotropin-releasing hormone; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging; AST=aspartate aminotransferase.
NUBEQA® (darolutamide) tablets, for oral use

Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1)].

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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.

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=594)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥ 3 %</td>
</tr>
<tr>
<td>Fatigue1</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see Clinical Pharmacology (12.3)]. Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)]. Animal embryo-fetal developmental toxicity studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary
The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males
Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1)].

Infertility

Males
Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m²). The effect of end stage renal disease (eGFR <15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)]. In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hypoplasia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION

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

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

Infertility

Advise male patients that NUBEQA may impair fertility [see Use in Specific Populations (8.3)].

Manufactured by: Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland

Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

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For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

6711101851
Investigators Prepare for the Next Wave of Immunotherapy Advances

by ANDREW SMITH

SINCE CHARU AGGARWAL, MD, MPH, helped conduct the first phase 1 trial of pembrolizumab (Keytruda) nearly a decade ago, she has been recognized as a pioneer in testing immunotherapy treatments for thoracic cancers. From this launchpad, her research focuses broadened to include liquid biopsies, expanding the knowledge bank of personalized care for patients.

Aggarwal is the Leslye M. Heisler Associate Professor for Lung Cancer Excellence at the University of Pennsylvania (UPenn) Perelman School of Medicine in Philadelphia. In her work at UPenn, Aggarwal conducts research in a variety of areas, particularly the development and validation of liquid biopsies designed not only for initial diagnosis, but also for the repeated evaluation of a treatment’s initial and ongoing efficacy.

“Dr Aggarwal has conducted some of the pioneering work in liquid biopsy research, work that has changed how we use liquid biopsies and increased our confidence in it as a routine tool,” Howard “Jack” West, MD, clinical executive director of AccessHope and associate clinical professor in the Department of Medical Oncology & Therapeutics Research at City of Hope in Duarte, California, said.

“She has also helped conduct and oversee some of the important retrospective database work that has shaped our ideas of optimal care for patients with KRAS mutations, determining whether they should receive immunotherapy alone or immunotherapy with chemotherapy,” said West, who has worked with Aggarwal for many years and hosts a podcast with her.

Benjamin Levy, MD, associate professor at Johns Hopkins University School of Medicine and clinical director of medical oncology at Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital in Baltimore, Maryland, echoed West’s praise for Aggarwal’s work in liquid biopsies.

“She has done some of the seminal work with liquid biopsies in advanced lung cancer,” he said. “Through her research, she has demonstrated that circulating tumor DNA [ctDNA] can be a very powerful tool in not only genotyping lung cancer patients, but also serving as a real-time surrogate or response in patients treated with targeted therapy and immunotherapy via longitudinal assessments with this platform.”

Levy described Aggarwal as incredibly persistent. “She doesn’t stop until the research question is answered,” he said. “When you combine that dedication with intelligence and ability to think out of the box and investigate ideas that others haven’t considered, you have a very successful researcher.”

Aggarwal is cochair of the 6th Annual International Congress on Immunotherapies in Cancer®, which will take place as a hybrid, interactive event on Saturday, December 11 at the InterContinental New York Times Square.

The 1-day conference, hosted by Physicians’ Education Resource®, LLC (PER®), will provide a comprehensive review of clinical trial-derived and real-world data that are most relevant to the application of cancer immunotherapy. Topics of particular attention will be new developments in biomarkers,
recent immunotherapy combinations, and strategies for mitigating adverse events (AEs).

Aggarwal and conference cochair Mario Szol, MD—who leads the melanoma program and coleads the cancer immunotherapy program at Yale Cancer Center, in New Haven, Connecticut—have assembled a team of experts to discuss recent findings in a host of subjects:

- Stratifying risk and predicting response to immunotherapeutic regimens in cancer management
- Correlating each immunotherapy’s mechanisms of action to its application in the treatment of malignancy
- Evaluating emerging data from clinical trials on the efficacy and safety of cancer immunotherapy regimens
- Implementing practical strategies for the immunotherapy management of solid and hematologic malignancies, along with the management of AEs

“There has been this wave of approvals in the past few years, starting with melanoma and lung cancer and moving to other tumor types,” Aggarwal said in an interview with OncologyLive. “At the same time, we are seeing approved uses for immunotherapy move from the metastatic setting to the neoadjuvant and adjuvant settings in diseases such as kidney cancer, lung cancer, and more. What I want the attendees to take out of this conference is practical information on how to apply chemotherapy or immunotherapy in the clinic, in the context of new clinical information and new clinical trials that have been presented at recent meetings.”

**PERSONALIZING APPROACHES TO TREATMENT**

Although neither of her parents were doctors, Aggarwal decided that she would make medicine her life’s work when she was 5 years old. The decision to specialize in cancer research was made when she was pursuing her master’s degree and had the opportunity to work on bone marrow transplants. Aggarwal’s principal research interests are strategies for improving decisions that will tailor treatments for each individual patient with cancer.

For example, she was recently the senior author of an analysis of the association of KRAS variant status and outcomes in patients who received immunotherapy alone vs those who received immunotherapy plus chemotherapy.1 The study compared outcomes among 1127 patients with advanced nonsquamous non–small cell lung cancer (NSCLC) with PD-L1 expression of 50% or greater, 573 of whom (50.8%) had KRAS-wild-type disease and 554 of whom (49.2%) had KRAS wild-type disease. Among patients with KRAS-mutant disease, overall survival (OS) did not differ between those treated with immune checkpoint inhibitor (ICI) monotherapy and chemoinmunotherapy; the median OS was 21.1 vs 20.0 months, respectively (adjusted HR, 1.03; 95% CI, 0.75-1.40; P = .78). Among patients with KRAS wild-type disease, those treated with ICI monotherapy had worse survival vs those treated with chemoinmunotherapy, although the difference was not statistically significant (median OS, 13.0 vs 19.3 months, respectively; adjusted HR, 1.19; 95% CI, 0.89-1.58; P = .06).

Aggarwal and her colleagues wrote that the results of the analysis suggest that patients with KRAS wild-type disease should get the combination of immunotherapy and chemotherapy, but the absence of any apparent survival benefit of adding chemotherapy to immunotherapy for patients with KRAS-mutant disease struck Aggarwal as an equally important finding.

“In my mind, the question is not who should get chemotherapy, but rather, who can avoid chemotherapy,” Aggarwal said. “With the explosion of immunotherapy, we can now deliver [agents] safely with a survival benefit for most of our patients. There will always be a subset [of patients who] cannot get immunotherapy, but for the vast majority of our patients, they can, and we can use testing to determine which patients can get immunotherapy alone. It’s only for a small subset of patients that we’re now using a combination of chemotherapy and immunotherapy.”

The molecular phenotyping needed to guide the cancer treatment by driver or resistance mutations has relied mostly on formalin-fixed, paraffin-embedded specimens from tissue biopsies. Investigative efforts from Aggarwal and others have demonstrated that materials shed by tumors that then reside in bodily fluids including urine, saliva, pleural effusion, cerebrospinal fluid, and especially blood, can provide much of the same information.2

Tumor analytes in blood include tumor-derived extracellular vesicles, circulating tumor cells, messenger RNA, microRNA, and ctDNA, which is contained in plasma cell-free DNA (cfDNA).

Several plasma cfDNA genotyping assays for NSCLC have been approved by the FDA for clinical practice, including assays based on polymerase chain reaction and next-generation sequencing (NGS).3 Available assays include the following (Table 1):
Immunotherapy

- Cobas EGFR Mutation Test, which was approved for the identification of EGFR driver mutations that may benefit from treatment with tyrosine kinase inhibitors (TKIs);
- Guardant360 CDx, which can detect mutations in EGFR, ALK, ROSI, BRAF, RET, MET, NTRK, KRAS, and ERBB2 (HER2) and is approved as a companion diagnostic for 3 agents in NSCLC; and
- FoundationOne Liquid CDx, which was approved in 2020 to detect more than 300 cancer-related genes and multiple genomic signatures such as tumor mutational burden and microsatellite instability.

Investigators have compared genotyping results acquired by tissue and plasma assays and found a high level of concordance. For example, Aggarwal and co-investigators at the UPenn, collected 112 plasma samples from 102 prospectively enrolled patients with advanced NSCLC and performed NGS of 70 genes. They then compared results with those obtained from tissue samples in 50 of the patients. Actionable EGFR mutations were detected in 24 tissue and 19 ctDNA samples, yielding concordance of 79%, with a shorter time interval between tissue and blood collection associated with increased concordance (P = .038). In another study designed to validate plasma-based cancer genotyping, orthogonal plasma- and tissue-based clinical genotyping across more than 750 patients demonstrated high accuracy and specificity. Positive percent agreement and negative percent agreement were greater than 99% and positive predictive values were 92% to 100%.

“There are still significant limitations. We cannot necessarily characterize the cell type or the architecture of a tumor with a liquid biopsy, which is still very necessary, so looking at tissue is extremely important,” Aggarwal said. “But I think plasma or liquid biopsies are going to be essential to give us information about the rest of the tumor. In fact, it sometimes gives us a clearer picture of the heterogeneous nature of the tumor, since we can get a sense of the cells that may have more of a metastatic potential and may have slightly different mutational profile. And we can actually gather that much better than we can do with a single, small biopsy.”

A PROMISING FUTURE FOR LIQUID BIOPSY

Liquid biopsies have other key advantages: They are cheaper, less painful for the patient, and take less time to analyze. Thus, they may be performed repeatedly and, in some cases, be used to determine both initial response to a treatment and when resistance begins to develop. For example, patients treated with TKIs for EGFR-mutated or ALK-rearranged NSCLCs can develop resistance mutations, which can appear in blood samples and obviate the need for repeated tissue biopsies.

Conversely, ctDNA testing can also detect when patients with cancer are responding to immunotherapy. A 2020 study analyzed pretreatment (n = 978) and on-treatment (n = 171) ctDNA samples from 16 advanced-stage tumor types from 3 phase 1/2 trials of durvalumab (Imfinzi), with or without the anti-CTLA-4 therapy, tremelimumab. Among patients on treatment, reductions in variant allele frequencies (VAF) and lower on-treatment VAF were independently associated with longer progression-free survival (PFS) and OS as well as a higher objective response rate.

Another potential use for liquid biopsies is early cancer detection, but tests developed to date are not sensitive enough to support such usage in NSCLC, according to current treatment guidelines. For a variety of reasons, the use of liquid biopsies has advanced further in the diagnosis and treatment of lung cancer than it has in many other tissue types.

“Lung cancer is really one of the leading subtypes of cancer where liquid biopsies are being used,” Aggarwal said. “That’s largely because there is a significant amount of ctDNA shed into the bloodstream in patients with advanced disease and also because lung cancer has so many different subtypes that now have actionable mutations that are targeted by particular drugs, where we can actually immediately act and say, ‘You have an EGFR mutation. I’m going to give you a pill that targets that’ or, ‘You have a MET exon 14 mutation, so I’m going to give you something that targets that.’ There’s just more actionality to lung cancer than there is to other diseases. But having said that, you know, breast cancer, [gastrointestinal] cancer, and [genitourinary] cancer are all now rapidly taking up these liquid biopsy tools and expanding the liquid biopsy space to really utilize it in the clinical setting.”

MANAGING IMMUNE-RELATED ADVERSE EVENTS

Another major topic of conversation at the International Congress on Immunotherapies in Cancer will be AEs associated with immunotherapy. Panelists will, of course, discuss evolving strategies for managing AEs—strategies that have significantly reduced the dangers that patients face from such treatments—and the evolving guidelines from the National Comprehensive Cancer Network, the Society for Immunotherapy of Cancer, and the American Society of Clinical Oncology. Panelists will also discuss the growing evidence that suggests some AEs have a positive effect: predicting response to immunotherapy.

“There is recent evidence suggesting that the presence of immune-related AEs [irAEs]...
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- Interact with expert thought leaders to evaluate best practice paradigms for the use of immunotherapeutics for the management of both solid tumors and hematologic malignancies
- Work through a series of challenging patient cases with renowned clinical experts, including Mario Sznol, MD, Charu Aggarwal, MD, and Jeffrey Weber, MD
- Hear expert analysis and commentary from leaders at the forefront of research about the future of immuno-oncology

**PROGRAM CHAIRS**

**Mario Sznol, MD**
Professor of Medicine (Medical Oncology)
Yale School of Medicine
Program Leader, Melanoma
Co-Leader, Cancer Immunology Program
Yale Cancer Center
New Haven, CT

**Charu Aggarwal, MD, MPH**
Leslye M. Heisler Associate Professor for Lung Cancer Excellence
Hospital of the University of Pennsylvania
Philadelphia, PA

**SAFETY PRECAUTIONS/PERSONAL ACCOUNTABILITY COMMITMENT**

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**ACKNOWLEDGMENT OF COMMERCIAL SUPPORT**

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in patients that receive immunotherapy may be related to better outcomes,” Aggarwal said. “It seems that this effect may depend on the grade of AE, although the research remains preliminary, but at least what we have now suggests that grade 2 and 3 AEs may actually be better in terms of predicting an improved outcome to immunotherapy, which I think is very interesting. It’s sort of reminiscent of the old days when we used to look at things like a rash from an EGFR inhibitor that would tell us that the drug is working.”

Indeed, some studies have found a strong connection between irAEs and response to immunotherapy. For example, a 2019 study by investigators from Madrid reported on 106 patients with various tumor types treated with either pembrolizumab or nivolumab (Opdivo) monotherapy. Of the 40 patients with irAEs, 33 (82.5%) experienced an objective response. Among the 66 cases without irAEs, 11 (16.6%) had an objective response (OR, 23.5; \(P < .000001\)). The median PFS was 10 months for patients with irAEs and 3 months for those without irAEs (HR, 2.2; \(P = .016\)); median OS was 32 months for patients with irAEs and 22 months for those without irAEs, but that difference was not statistically significant.  

Although Aggarwal believes that most people who spent the last 15 months attending virtual conferences have developed severe cases of Zoom fatigue and long for a return to traditional face-to-face communication, she also believes that virtual conferences have some significant advantages and that, going forward, conferences will adopt a hybrid model that offers the best of both worlds.

“For one thing, virtual conferences increase the reach that a conference has. [Faculty] can engage [with] audiences from different time zones and different countries [making nearly] any conference a global event,” Aggarwal said. “Everyone wants to welcome our live conferences back, and I think as the Delta variant decreases, people will adopt a hybrid model that offers the best of both worlds.

Getting Back Out There

Virtual conferences, no matter how well done, do not offer the same opportunity for personal connections or the sorts of one-on-one conversations that have long ranked among the most valuable aspect of conferences. The in-person conference also offers another opportunity that Aggarwal cherishes: the opportunity to travel.

“Traveling is my ultimate hobby, although it has been almost entirely suspended by the COVID-19 pandemic, and I’m greatly looking forward to getting back to it,” Aggarwal said. “I love travel for its own sake and because it ties in with one of my other major hobbies, which is photography. It has been hard to go so long without really going anywhere. Fortunately, I have had even more time to pursue my other 2 hobbies—cooking and riding my Peloton—during the pandemic.”

REFERENCES


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Frontline Durvalumab/Chemotherapy, With or Without Tremelimumab, Improves PFS in Advanced NSCLC

by GINA MAURO

THE FIRST-LINE COMBINATION OF durvalumab (Imfinzi) and chemotherapy, with or without tremelimumab, led to a statistically significant improvement in progression-free survival (PFS) compared with chemotherapy alone in patients with metastatic non–small cell lung cancer (NSCLC). Data from the phase 3 POSEIDON trial (NCT03164616) were presented during the International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer.

The median PFS with durvalumab/chemotherapy was 5.5 months (95% CI, 4.7-6.5) compared with 4.8 months (95% CI, 4.6-5.8) for chemotherapy alone, leading to a 26% reduction in the risk of disease progression or death (HR, 0.74; 95% CI, 0.62-0.89; P = .00093).

However, the median overall survival (OS) was 13.3 months (95% CI, 11.4-14.7) with durvalumab/chemotherapy and 11.7 months (95% CI, 10.5-13.1) with chemotherapy alone—a difference that was not found to be statistically significant (HR, 0.86; 95% CI, 0.72-1.02; P = .07581).

Conversely, when tremelimumab was added to the durvalumab/chemotherapy regimen, both the PFS and OS benefits of chemotherapy were statistically significant, explained lead study author Melissa L. Johnson, MD, who presented the data virtually in a press briefing during the meeting.

Specifically, the median PFS was 6.2 months with the triplet (95% CI, 5.0-6.5) vs 4.8 months (95% CI, 4.6-5.8) with chemotherapy alone (HR, 0.72; 95% CI, 0.60-0.86; P = .00031). The median OS was 14.0 months (95% CI, 11.7-16.1) and 11.7 months (95% CI, 10.5-13.1) in the 3-drug and chemotherapy-alone arms, respectively (HR, 0.77; 95% CI, 0.65-0.92; P = .00304).

“We noticed an improved separation of the curves with the addition of tremelimumab, and improvement in both the 12-month PFS as well as the 24-month OS landmark analysis over what was seen with durvalumab plus chemotherapy,” Johnson, program director of Lung Cancer Research at Sarah Cannon Research Institute, said.

“Durvalumab plus tremelimumab plus chemotherapy represents a potential new frontline treatment option for patients with metastatic NSCLC.”

Although PD-1/PD-L1 inhibitors have transformed the treatment paradigm of advanced NSCLC, both as single agents and in combination with chemotherapy, an unmet need remains for this population. The addition of CTLA-4 inhibition to PD-L1 antibodies and chemotherapy, however, could confer further clinical and long-term survival benefit in select patient subgroups.

In the international, open-label, multicenter POSEIDON trial, investigators explored durvalumab, with or without tremelimumab, in combination with investigator’s choice of chemotherapy in the frontline treatment of patients with squamous or nonsquamous metastatic NSCLC (n = 1013). Patients were randomized 1:1:1 to receive durvalumab 1500 mg plus chemotherapy every 3 weeks for 4 cycles, followed by maintenance durvalumab 1500 mg every 4 weeks plus pemetrexed until disease progression (n = 330); durvalumab 1500 mg plus tremelimumab 75 mg and chemotherapy every 3 weeks for 4 cycles, followed by maintenance durvalumab 1500 mg every 4 weeks plus tremelimumab 75 mg at week 16 only, and pemetrexed until disease progression (n = 335); or platinum-based
chemotherapy every 3 weeks for up to 6 cycles, followed by maintenance pemetrexed until disease progression (n = 332).

Chemotherapy regimens included gemcitabine plus carboplatin or cisplatin for those with squamous histology, pemetrexed plus carboplatin or cisplatin for those with nonsquamous disease, or nab-paclitaxel (Abraxane) plus carboplatin for either histology.

To be eligible for enrollment, patients had to have stage IV NSCLC without EGFR or ALK alterations and an ECOG performance status of 0 or 1, and must not have received prior systemic therapy for metastatic disease. Patients were stratified by PD-L1 expression (tumor cells ≥ 50% vs < 50%), disease stage (stage IVA vs IVB), and histology.

The primary end points of the trial were PFS by blinded independent central review (BICR) and OS for durvalumab/chemotherapy vs chemotherapy alone. Secondary outcome measures were PFS by BICR and OS, as well as OS in patients with blood tumor mutational burden measuring at least 20 mutations per megabase for durvalumab/tremelimumab plus chemotherapy vs chemotherapy alone.

Additional outcome measures included objective response rate (ORR), duration of response (DOR), and best objective response by BICR, as well as 1-year PFS rate, health-related quality of life, safety, and tolerability.

Additional findings presented at the meeting showed that in the durvalumab/chemotherapy and chemotherapy-alone arms, the 1-year PFS rates were 24.4% and 13.1%, respectively. The 2-year OS rates were 29.6% and 22.1%, respectively. With the addition of tremelimumab to durvalumab/chemotherapy, the 1-year PFS rate was 26.6% and the 2-year OS rate was 32.9%.

Johnson said that the addition of tremelimumab to durvalumab/chemotherapy appeared to have the highest benefit in patients with nonsquamous histology (TABLE).

The confirmed ORRs were 41.5% with durvalumab/chemotherapy, 38.8% with durvalumab/tremelimumab plus chemotherapy, and 24.4% with chemotherapy alone. The odds ratio was 2.26 (95% CI, 1.61-3.19) between durvalumab/chemotherapy and chemotherapy alone and 2.00 (95% CI, 1.43-2.81) between durvalumab/tremelimumab plus chemotherapy and chemotherapy alone.

Additionally, the DOR was 7.0 months (95% CI, 5.7-9.9), 9.5 months (95% CI, 7.2-not estimable), and 5.1 months (95% CI, 4.4-6.0) for durvalumab/chemotherapy, durvalumab/chemotherapy plus tremelimumab, and chemotherapy alone, respectively. At 12 months, 38.9%, 49.7%, and 21.4% of these patients maintained a response, respectively.

Regarding safety, the trial investigators observed no unexpected safety signals, and most adverse effects (AEs) were driven by chemotherapy.

All-grade, all-cause AEs occurred in 96.1%, 97.3%, and 96.1% of patients who received durvalumab/chemotherapy, durvalumab/chemotherapy plus tremelimumab, and chemotherapy alone, respectively; the rates of grade 3/4 AEs in these groups were 54.8%, 53.3%, and 51.7%, respectively. Serious AEs occurred in 40.1% of patients receiving durvalumab/chemotherapy, 44.2% of those receiving durvalumab/chemotherapy plus tremelimumab, and 35.1% of those receiving chemotherapy alone.

Treatment discontinuation (20.4%, 22.1%, and 15.3%, respectively) and death rates (10.2%, 12.4%, and 9.0%, respectively) were reported.

### TABLE. Efficacy for Nonsquamous and Squamous Histology in Phase 3 POSEIDON Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Durvalumab + chemotherapy (n = 209)</th>
<th>Durvalumab + tremelimumab + chemotherapy (n = 214)</th>
<th>Chemotherapy (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.4 (4.7-7.4)</td>
<td>6.8 (6.1-8.5)</td>
<td>5.5 (4.8-6.4)</td>
</tr>
<tr>
<td>HR (vs chemotherapy alone)</td>
<td>0.77 (95% CI, 0.61-0.96)</td>
<td>0.66 (95% CI, 0.52-0.84)</td>
<td>NA</td>
</tr>
<tr>
<td>1-year PFS rate</td>
<td>32.2%</td>
<td>34.6%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>44.3%</td>
<td>45.5%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>10.6 (6.6-NE)</td>
<td>16.4 (9.3-NE)</td>
<td>6.0 (4.4-8.7)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.8 (11.8-18.3)</td>
<td>17.2 (14.9-21.8)</td>
<td>13.1 (10.6-15.1)</td>
</tr>
<tr>
<td>HR (vs chemotherapy alone)</td>
<td>0.82 (95% CI, 0.66-1.03)</td>
<td>0.70 (95% CI, 0.56-0.87)</td>
<td>NA</td>
</tr>
<tr>
<td>1-year OS rate</td>
<td>35.4%</td>
<td>41.4%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Durvalumab + chemotherapy (n = 128)</th>
<th>Durvalumab + tremelimumab + chemotherapy (n = 124)</th>
<th>Chemotherapy (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>4.7 (4.6-6.3)</td>
<td>4.6 (3.9-5.1)</td>
<td>4.6 (4.2-4.8)</td>
</tr>
<tr>
<td>HR (vs chemotherapy alone)</td>
<td>0.68 (95% CI, 0.52-0.90)</td>
<td>0.77 (95% CI, 0.58-1.01)</td>
<td>NA</td>
</tr>
<tr>
<td>1-year PFS rate</td>
<td>10.9%</td>
<td>12.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>37.3%</td>
<td>27.4%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>5.5 (4.9-6.7)</td>
<td>5.6 (4.3-7.2)</td>
<td>4.8 (3.7-5.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>11.5 (9.4-14.0)</td>
<td>10.4 (8.4-12.7)</td>
<td>10.5 (8.0-11.7)</td>
</tr>
<tr>
<td>HR (vs chemotherapy alone)</td>
<td>0.84 (95% CI, 0.64-1.10)</td>
<td>0.88 (95% CI, 0.68-1.16)</td>
<td>NA</td>
</tr>
<tr>
<td>1-year OS rate</td>
<td>20.6%</td>
<td>18.1%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

DOR, duration of response; NA, not applicable; NE, not estimable; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.
Lurbinectedin/Doxorubicin Misses OS End Point But Shows Superior Safety in Relapsed SCLC

by COURTNEY MARABELLA

THE COMBINATION OF LURBINECTEDIN (Zepzelca) and doxorubicin elicited comparable efficacy to that of standard-of-care (SOC) vincristine, cyclophosphamide, and doxorubicin (CAV) or topotecan in patients with relapsed small cell lung cancer (SCLC), missing the primary end point of the phase 3 ATLANTIS trial (NCT02566993).

Despite this, the doublet showcased a superior safety and tolerability profile.

Results presented during the International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer showed that the median overall survival (OS) in the intention-to-treat population was 8.6 months (95% CI, 7.1-9.4) in the investigative arm vs 7.6 months (95% CI, 6.6-8.2) in the control arm (HR, 0.967; 95% CI, 0.815-1.148; P = .7032). The mean OS in these arms was 10.6 months and 9.9 months, respectively.

“We did not see a [significant] improvement in efficacy, and the trial did not meet the primary end point; however, we did confirm the safety profile [of lurbinectedin] even when adding doxorubicin,” said lead study author Luis Paz-Ares, MD, PhD, during the presentation. Paz-Ares is chair of the Medical Oncology Department at the Hospital Universitario 12 de Octubre, an associate professor at the Universidad Complutense de Madrid, and head of the Lung Cancer Unit at the National Oncology Research Center in Spain. “Lurbinectedin was more tolerable, particularly in terms of myelosuppression, than SOC. More importantly, new combinations of lurbinectedin and other cytotoxic agents are currently being explored in this setting.”

SCLC is the most aggressive form of lung cancer and mostly occurs in smokers, according to Paz-Ares. Although the disease has proved to be sensitive to chemotherapy and radiation, responses are short and those who relapse have a survival of approximately 6 to 8 months. Much has been learned about the biology of SCLC, but treatment options remain limited, Paz-Ares added.

In June 2020, the FDA approved single-agent lurbinectedin for the treatment of adult patients with metastatic SCLC with disease progression following platinum-based chemotherapy, at a dose of 3.2 mg/m² every 3 weeks. The regulatory decision was based on results from a phase 2 basket trial (NCT02454972), in which the agent elicited higher response rates in patients who were platinum sensitive and had a chemotherapy-free interval (CTFI) of 90 days or more compared with those who were platinum resistant and had a CTFI of less than 90 days; these rates were 45.0% and 22.2%, respectively.

A phase 1 dose-escalation study (NCT01970540) was conducted to investigate lurbinectedin in combination with doxorubicin, based on synergistic activity observed in in vitro assays. Results showed that the combination elicited an overall response rate (ORR) of 36%, a median progression-free survival of 3.3 months, and a median OS of 7.9 months as a second-line treatment for patients with SCLC. When the investigators excluded patients with refractory disease with a CTFI of 30 days or less, the ORR achieved with the regimen was 46%, the median PFS was 5.1 months, and the median OS was 10.2 months. “These results were promising compared with historical data for topotecan and CAV,” Paz-Ares noted.

Based on results from this study, investigators determined that the recommended dosing for the regimen in the second-line setting should be 40 mg/m² doxorubicin and 2.0 mg/m² lurbinectedin given on day 1 of every 3-week cycle. Investigators launched the ATLANTIS trial to examine the combination vs standard of care.

To be eligible for enrollment, patients had to have a confirmed diagnosis of SCLC and have received 1 prior line of chemotherapy. Additionally, they needed to have an ECOG performance status of 2 or less and measurable disease per RECIST 1.1 criteria. Those with a CTFI of less than 30 days were excluded.

The investigators randomized eligible patients 1:1 to the experimental arm, where...
IN THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA
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SARCLISA is an anti-CD38 therapy proven to deliver superior PFS (median PFS of 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P=0.0010). SARCLISA also demonstrated a significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)*

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®)

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.1
CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; NCCN=National Comprehensive Cancer Network; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Indication
SARCLISA (isatuximab-irfc) 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.

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.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Choose SARCLISA + Pd to Offer Improved Outcomes to More Patients vs Pd Alone

Studied in the phase 3 ICARIA-MM trial, which included

patients with poor prognostic factors.

Based on the ICARIA-MM trial, SARCLISA + Pd is a treatment choice for patients with relapsed refractory multiple myeloma

- Who have received at least 2 prior therapies, including lenalidomide and a PI
- Who may have renal impairment (creatinine clearance <60 mL/min/1.73 m²), high cytogenetic risk, or a history of COPD or asthma
- Who may have poor performance status or are ≥75 years of age
- Who are refractory to lenalidomide, a PI, or both

STUDY DESIGN: ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint; ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.

PATIENT CHARACTERISTICS: The median patient age was 67 years (range, 36 to 86), and 20% of patients were ≥75 years of age. Ten percent of patients entered the study with a history of COPD or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 34%. The ISS stage at study entry was I in 37%, II in 36%, and III in 25% of patients. Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14), and t(14;16) were present in 12%, 8%, and 2% of patients, respectively. The median number of prior lines of therapy was 3 (range, 2 to 11). All patients received a prior PI, all patients received prior lenalidomide, and 56% of patients received prior stem cell transplantation; the majority of patients (93%) were refractory to lenalidomide, 76% to a PI, and 73% to both an immunomodulator and a PI.

Important Safety Information (cont’d)

Infusion-Related Reactions (cont’d)

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, 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.
SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd.

At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.

SARCLISA + Pd showed a significant increase in ORR

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60.4%</strong> ORR</td>
<td><strong>35.3%</strong> ORR</td>
</tr>
<tr>
<td><em>P&lt;0.0001</em></td>
<td></td>
</tr>
<tr>
<td><strong>31.8% ≥VGPR</strong></td>
<td><strong>8.5% ≥VGPR</strong></td>
</tr>
<tr>
<td>~4× increase</td>
<td></td>
</tr>
<tr>
<td>35 days</td>
<td>Median time to first response among responders 58 days</td>
</tr>
</tbody>
</table>

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

Important Safety Information (cont’d)

**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%).

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Important Safety Information (cont’d)

Neutropenia (cont’d)
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 accompanying brief summary of full Prescribing Information.


SANOFI GENZYME
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SARCLISA® Rx Only (isatuximab-irbc) injection, for intravenous use

Brief Summary of Prescribing Information

1. Indications and Dosage

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

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Administer the solution for infusion using aseptic technique as follows:

For information concerning drugs given in combination with SARCLISA and pomalidomide administration.

Prepare the solution for infusion using aseptic technique as follows:

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadie (PBD), or polyurethane (PU)) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will allow for the infusion to be completed (see Table 2).
- Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C–8°C, followed by 8 hours (including the infusion) at room temperature.
- Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.

Infusion Rate

Following infusion, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only in the absence of infusion-related reactions (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)).

Table 2: Infusion Rates of SARCLISA Administration

<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.

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.
- Dihydropyrimidine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backdose, before SARCLISA and pomalidomide administration.

Administer the following premedications to patients 15 to 60 minutes prior to starting a SARCLISA infusion.

2.3 Dose Modifications

No dose reduction of SARCLISA is recommended. Dose delay may be required to obtain recovery of blood counts in the event of hematologic toxicity (see Warnings and Precautions (5.2, 5.4)). For information concerning drugs given in combination with SARCLISA, see manufacturer’s prescribing information. For other medicinal products that are administered with SARCLISA and for at least 5 months after the last dose of SARCLISA, consider only in the absence of infusion-related reactions (see Use in Specific Populations (8.1, 8.3)). 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.

6.1 Clinical Trials Experience

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

Multiple Myeloma

The safety 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/mm3, absolute neutrophil count ≥1.5 x 10⁹/mm3, creatinine clearance ≥30 ml/min (MDRD formula), and AST and or ALT ≤3 x ULN. Patients received SARCLISA 10 mg/kg intravenously, with the first dose of SARCLISA given as 50 mL/hour then increased by 25 mL/hour every 30 minutes. Following dilution, administer the SARCLISA infusion for at least the first 4 infusions.

5. Embry-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 (see Use in Specific Populations (8.1, 8.3)). 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.

5.1 Infusion-Related Reactions

SARCLISA is contraindicated in patients with severe hypersensitivity to any component of SARCLISA or any of its excipients (see Warnings and Precautions (5.1)).

5.2 Warnings and Precautions

5.2.1 5% 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 98% of cases. The most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypotension and tachycardia (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 rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 (see Dosage and Administration (2.5)). In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA therapy if a grade 3 or higher infusion-related reaction occurs and institute appropriate medical management.

5.2 Neutropenia

SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormalities) occurred in 90% 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. Febrile neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%) (see Adverse Reactions (6.1)). Manage complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs and symptoms of upper respiratory tract infections. 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 per 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 Isa-Pd arm (range 3%-6%); 58% male, 76% white, and 14% Asian. Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions occurred 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 included pneumonia and other infections (3%)). Permanent discontinuation due to an adverse reaction (grades 1-4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.6%). In addition, SARCLISA and pomalidomide and dexamethasone (Pd) arm, breast angiosarcoma (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, as per International Myeloma Working Group (IMWG) guidelines.

5.4 Laboratory Test Interference

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antioglobulin 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 results 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 discontinuing SARCLISA treatment if positive to 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 diithiothreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs should be given as per local blood bank practices (see Drug Interactions (7.1)).

Interference with Serum Protein Electrophoresis and Immunofixation

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 may impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein (see Drug Interactions (7.1)).

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 practice.

Multiple Myeloma

The safety 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/mm3, absolute neutrophil count ≥1.5 x 10⁹/mm3, creatinine clearance ≥30 ml/min (MDRD formula), and AST and/or ALT ≤3 x ULN. Patients received SARCLISA 10 mg/kg intravenously, with the first dose of SARCLISA given as 50 mL/hour then increased by 25 mL/hour every 30 minutes. Following dilution, administer the SARCLISA infusion for at least the first 4 infusions.

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

### Table 3: Adverse Reactions (≥10%) in Patients 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=152)</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>38 (1.3)</td>
<td>1.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>31 (2.1)</td>
<td>22</td>
<td>3</td>
<td>16</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection†</td>
<td>57 (9)</td>
<td>0</td>
<td>42</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12 (11.3)</td>
<td>1.3</td>
<td>2</td>
<td>1.3</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea†</td>
<td>17 (15.5)</td>
<td>0</td>
<td>12</td>
<td>1.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (2.2)</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (1.3)</td>
<td>0</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTCAE version 4.03</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| *Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumoconiosis (pneumoconiosis).
| †Upper respiratory tract infection includes bronchiolitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, macropharyngeal syndrome, mononucleosis, pneumonia viral, 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 hematologic laboratory abnormalities in ICARIA-MM.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter (% of Subjects)</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>151 (99)</td>
<td>49 (32)</td>
<td>145 (91)</td>
<td>41 (28)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>146 (96)</td>
<td>37 (24)</td>
<td>137 (82)</td>
<td>57 (38)</td>
<td>48 (31)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>140 (92)</td>
<td>64 (44)</td>
<td>137 (82)</td>
<td>57 (38)</td>
<td>48 (31)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>137 (82)</td>
<td>64 (44)</td>
<td>137 (82)</td>
<td>57 (38)</td>
<td>48 (31)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>127 (84)</td>
<td>46 (31)</td>
<td>118 (79)</td>
<td>22 (15)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</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 56 patients (36%) 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%, 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 55 minutes.

In a separate study (TCD 14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 49% 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.

**Infusions**

In ICARIA-MM, the incidence of Grade 3 or higher reactions was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe reaction with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 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, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent ADAs 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-CD38 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 antihuman globulin crossmatches in patients treated with SARCLISA (see Warnings and Precautions (5.4)).

**Interference with Serum Protein Electrophoresis and Immunofixation Tests**

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy. Pomalidomide is only available through a REMS program.

**Clinical Considerations**

Fetal/neonatal reactions

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Refer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.
In the analysis of the safety population, treatment-related adverse effects (TRAEs) of any grade were reported in 88.4% of patients in the investigative arm (n = 303) and 92.0% of those in the control arm (n = 289). Notably, lower rates of grade 3 or greater TRAEs were reported in the lurbinectedin arm vs the control arm, at 47.2% vs 75.4%. Moreover, lower rates of grade 4 TRAEs were reported with lurbinectedin vs SOC (16.2% vs 54.7%); the same was true regarding grade 3 or higher serious AEs (12.5% vs 28.7%), treatment discontinuation associated with AEs (7.6% vs 15.6%), and deaths associated with AEs (0.3% vs 3.5%). Additionally, lower rates of grade 3 or higher hematologic AEs were reported in the investigative arm vs the control arm, including anemia (14.5% vs 31.1%), neutropenia (37.0% vs 69.2%), and thrombocytopenia (13.9% vs 31.1%).

The most frequently reported grade 3 or higher nonhematologic AE was fatigue; this was experienced by 8.6% of patients in the investigative arm compared with 10.7% of those in the control arm.

**Additional data showed that the median progression-free survival (PFS) was 5.3 months (95% CI, 2.7-9.3) in patients with brain metastases.** The PFS rate at 6 months was 31.3% (95% CI, 25.8%-36.9%) in the investigative arm vs 24.4% (95% CI, 19.1%-30.1%) in the control arm (P = .0851). At 12 months, these rates were 10.8% (95% CI, 7.1%-15.3%) and 4.4% (95% CI, 2.1%-8.1%), respectively (P = .0129).

In patients with brain metastases previously treated with radiation or surgery, the findings from a post hoc analysis of the ongoing phase 1/2 CodeBreaK 100 trial (NCT03600883) were presented during the International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer.

**At a median follow-up of 12 months, sotorasib led to a confirmed objective response rate (ORR) per RECIST 1.1 criteria of 25% in patients with NSCLC and stable brain metastases previously treated with radiation or surgery.** The findings from an FDA-approved trial of grade 4 TRAEs were reported with lurbinectedin in patients with NSCLC and stable brain metastases, as determined by an FDA-approved test. Patients must have received at least 1 prior systemic therapy.

Sotorasib is a first-in-class, selective, irreversible small molecule inhibitor of KRAS G12C that received accelerated approval from the FDA on May 28, 2021, for the treatment of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test. Patients must have received at least 1 prior systemic therapy. The FDA based their decision on findings from the CodeBreaK 100 trial, in which sotorasib induced an ORR of 37.1% (95% CI, 28.6%-46.2%), a median PFS of 6.8 months (95% CI, 5.1-8.2), and a median OS of 12.5 months (95% CI, 10.0-not estimable) in the efficacy population (N = 124).
Patients with active brain metastases were excluded from the CodeBreaK 100 trial; however, patients with stable, asymptomatic brain metastases were eligible for inclusion. Study investigators enrolled patients with locally advanced or metastatic NSCLC who harbored a \textit{KRAS} G12C mutation as assessed by central testing of tumor biopsies and who had progressed on prior standard therapies. Patients received a 960-mg oral dose of sotorasib daily until disease progression.

The primary end point of the study was ORR per RECIST 1.1 criteria by blinded-independent central review. Key secondary end points included duration of response, DCR, time to response, PFS, OS, and safety.

In the posthoc analysis, the investigators retrospectively evaluated responses to sotorasib in target and nontarget stable brain metastases. They defined target lesions as measurable lesions suitable for accurate repeated measurements, and nontarget lesions as lesions too small for accurate repeated measurements.

In patients with baseline brain metastases (n = 40), the median age was 67 years (range, 46-83), and 90% of patients were current or former smokers. Most patients had an ECOG performance status of 1 (75%), and nearly a quarter had 3 metastatic sites (27%). Sixteen patients (40%) had received 1 prior line of systemic anticancer therapy. Regarding local therapies for the brain, 65% of patients had received prior radiotherapy, 20% had undergone surgery, and 12% had received radiotherapy and surgery.

In patients without baseline brain metastases (n = 134), the median age was 65 years (range, 37-86), and 90% of patients were current or former smokers. Most patients had an ECOG performance status of 1 (71%) and 1 metastatic site (45%) and had received 1 prior line of systemic anticancer therapy (41%). Regarding local therapies for the brain, 2 patients had received prior radiotherapy and 1 had undergone surgery. Of note, these local therapies may have been historic and led to sufficient removal of the brain metastasis so that the patient did not have a confirmed brain metastasis at baseline during the time of enrollment.

Additional findings from the study demonstrated that the median tumor reduction rate was 27% in patients with brain metastases compared with 40% in patients without brain metastases.

Central Response Assessment in Neuro-Oncology (RANO) analysis demonstrated that 9.2% (n = 16/174) of patients had baseline scans, as well as at least 1 on-treatment evaluable scan, which confirmed that 9 patients had 1 lesion, 2 patients had 4 lesions, and 5 patients had 5 or more lesions.

In patients with target and nontarget central nervous system (CNS) lesions (n = 3), no patients achieved a complete response (CR), 33% (n = 1) achieved stable disease (SD), and 67% (n = 2) had progressive disease (PD). In patients with nontarget CNS lesions (n = 13), 15% (n = 2) achieved a CR, 85% (n = 11) achieved SD, and no patients had PD. In all evaluable patients with brain metastases per RANO analysis (n = 16), 13% (n = 2) achieved a CR, 75% (n = 12) achieved SD, and 13% (n = 2) had PD.

Regarding safety, 20% (n = 8) of patients with baseline brain metastases reported grade 3 treatment-related adverse effects (TRAEs) with sotorasib compared with 19% (n = 26) of patients without baseline brain metastases. Grade 4 TRAEs were reported in 0 patients vs 2 patients (1.5%), respectively. No grade 5 TRAEs occurred in either arm.

The ongoing phase 1/2 CodeBreaK 101 trial (NCT04185883) is evaluating sotorasib in combination with other anticancer therapies including pembrolizumab (Keytruda), trametinib, and more, in patients with \textit{KRAS} G12C-mutated advanced solid tumors and active untreated brain metastases.¹

### TABLE. Efficacy Results in CodeBreaK100 Trial¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>With BM (n=40)</th>
<th>Without BM (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>25.0%</td>
<td>42.0%</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.3 (2.7-9.3)</td>
<td>6.7 (5.3-8.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>8.3 (7.3-12.5)</td>
<td>13.6 (10.0-NE)</td>
</tr>
<tr>
<td>Median tumor reduction</td>
<td>27%</td>
<td>40%</td>
</tr>
<tr>
<td>DCR</td>
<td>77.5%</td>
<td>84.1%</td>
</tr>
</tbody>
</table>

BM, brain metastases; DCR, disease control rate; NE, not estimable; OS, overall survival; PFS, progression-free survival.

¹ For a full list of references, see the article at bit.ly/2YGEqci.

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Mobocertinib Elicits Efficacy in Advanced EGFR Exon 20 Insertion+ NSCLC Regardless of Prior Immunotherapy

by GINA MAURO

MOBOCERTINIB (EXKIVITY) DEMONSTRATED CLINICAL activity in patients who received previous platinum treatment (PPP) with EGFR exon 20 insertion mutation-positive non–small cell lung cancer (NSCLC), whether or not they had received a prior PD-1/PD-L1 inhibitor. Findings from the phase 1/2 trial (NCT02716116) were presented during the International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer. Results showed that in the overall PPP subset (n = 114), the confirmed overall response rate (ORR via IRC) was 28% (95% CI, 20%-37%) and the disease control rate (DCR) was 78% (95% CI, 69%-85%). Additionally, among those in the PPP subset who had received prior PD-1/PD-L1 therapy (n = 48), the confirmed ORR via IRC was 25% (95% CI, 14%-40%) and was 30% (95% CI, 20%-43%) in those who had not received prior checkpoint blockade (n = 66).

The confirmed ORR via investigator-assessment was in the overall subset was 38% (95% CI, 24%-53%) and 33% (95% CI, 22%-46%), respectively.

“The safety profile of mobocertinib was consistent with the EGFR TKI class and manageable in both populations,” said lead study author Pasi A. Jänne, MD, PhD, who is director of the Lowe Center for Thoracic Oncology, Belfer Center for Applied Cancer Science, and Chen-Huang Center for EGFR Mutant Lung Cancer at Dana-Farber Cancer Institute in Boston, Massachusetts. Jänne is the 2021 Giants of Cancer Care® award winner in the lung cancer category. “These results suggest that mobocertinib is effective in platinum-pre-treated patients that have an EGFR exon 20 insertion mutation, regardless of the sequence of treatment with prior anti-PD(L)-1 therapies.”

On September 15, 2021, the FDA granted accelerated approval to mobocertinib for adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.2

Up to 12% of patients with EGFR-mutated NSCLCs have EGFR exon 20 insertion mutations.3 Mobocertinib is an oral, first-in-class, irreversible EGFR tyrosine kinase inhibitor targeting EGFR exon 20 insertion mutations in NSCLC and represents the first approved targeted agent for this specific patient population in the United States.

In the 3-part, phase 1/2 trial, investigators are exploring the efficacy and safety of mobocertinib in PPP with locally advanced or metastatic NSCLC who have EGFR in-frame exon 20 insertion mutations, in subsets with and without prior PD-1/PD-L1 inhibitors. The study also consists of dose-escalation, -expansion, and -extension (EXCLAIM) cohorts.

From all 3 trial parts, patients who had previously received platinum-based chemotherapy were included. All had an ECOG performance status of 0 to 1 and had received at least 1 prior line of therapy for locally advanced or metastatic disease. Mobocertinib was administered at 160 mg daily.

The primary end point was confirmed ORR per RECIST 1.1 criteria as assessed by an IRC; secondary outcome measures were investigator-assessed ORR, IRC-assessed DCR, duration of response (DOR), and PFS. Overall survival (OS) was also assessed. All patients who received at least 1 dose of mobocertinib were evaluable for safety.

Part 1 of the trial, the dose-escalation phase, was a 3 + 3 design of patients with advanced NSCLC and an ECOG performance score of 0 to 2; six patients had prior platinum-based therapy.

Part 2 was the expansion phase, in which mobocertinib was given at 160 mg daily. The primary end point was ORR via RECIST 1.1 criteria; secondary end points were safety, tolerability, pharmacokinetics, and efficacy.

Part 3 of the trial, the EXCLAIM extension cohort, included patients with previously treated EGFR exon 20 insertion mutation-positive disease (n = 96; prior PPP [n = 86]).

There are 6 cohorts within part 2 of the study (FIGURE): those with EGFR exon 20 insertion mutations who were refractory to prior platinum-based therapy refractory EGFR exon 20 insertion mutations with no active measurable central nervous system (CNS) metastases (cohort 1); refractory HER2 exon 20 insertion or point mutations, and no active, measurable CNS metastases (cohort 2); refractory EGFR or HER2 exon 20 insertions or point mutations with measurable active CNS metastases (cohort 3); treatment-naïve or refractory, other EGFR mutations with or without T790M mutations, and uncommon EGFR mutations (cohort 4); refractory EGFR exon 20 insertion mutations with prior response to an EGFR TKI (cohort 5); treatment-naïve EGFR exon 20 insertion mutations (cohort 6); and refractory other tumor types (non-NSCLC) with EGFR/HER2 mutations (cohort 7).

The findings presented at the conference comprised all PPPs from all 3 trial parts (n = 114). The data cutoff date was November 1, 2020.

In the PPP population, 49 patients (43%) had received prior immunotherapy, either as monotherapy or in combination with chemotherapy. Among those who had received prior PD-1/PD-L1 therapy (n = 48), 32 (67%) had received at least 2 prior lines of systemic anticancer therapy and 28 (58%) had immunotherapy as their most recent treatment.

The median age was 60 years (range, 27-84), and 66% of patients were female; 60% of patients were Asian and the majority (98%) had adenocarcinoma. Most patients (75%) had an ECOG performance status of 0.
1 and were never smokers (71%). Patients had received 1 (41%), 2 (32%), or more than 3 (27%) prior systemic anticancer regimens. The median number of prior regimens was 2. Thirty-five percent of patients had brain metastases at baseline.

Additional findings showed that, in the PPP subset of patients who did and did not receive PD-1/PD-L1 inhibition, the median DOR with mobocertinib was 17.5 months (95% CI, 3.7–not estimable [NE]) and 11.0 months (95% CI, 3.8–17.5), respectively; the DOR at 6 months or more via IRC was 58% and 60%, respectively. The confirmed DCR in this subset who had previously received PD-1/PD-L1 inhibition was 77% (95% CI, 63%–88%) compared with 79% (95% CI, 67%–88%) for those who had not received prior checkpoint inhibitors.

The median PFS in each group was similar at 7.4 months (95% CI, 5.5–21.1) and 7.3 months (5.4–10.2), respectively. The respective median OS was 21.1 months (95% CI, 13.1–NE) and 24.0 months (95% CI, 13.1–NE).

There were no marked differences between the 2 cohorts regarding best change from baseline in target lesion volume and duration of treatment in confirmed responders, both by IRC assessment, Jänecke noted.

Regarding safety, treatment-related adverse events (TRAEs) occurred in 100% of patients with and patients without prior PD-1/PD-L1 inhibitor therapy. Grade 3 or higher TRAEs occurred in 58% and 39% of patients, respectively, and serious treatment-emergent adverse events (TEAEs) in 54% and 45% of patients, respectively.

Furthermore, drug discontinuations due to TEAEs occurred in 21% of patients who had previously received PD-1/PD-L1 inhibition and in 14% of those who had not received the class of agents. TEAE-related dose modification rates were 77% and 55%, respectively.

Some TRAEs that occurred in 20% or more patients in the prior or no PD-1/PD-L1 treatment cohorts included: diarrhea (94% vs 89%, respectively), rash (42% vs 47%), paronychia (27% vs 45%), decreased appetite (33% vs 36%), vomiting (35% vs 26%), increased blood creatinine (23% vs 27%), anemia (21% vs 15%), nausea (42% vs 29%), dry skin (35% vs 27%), stomatitis (21% vs 26%), pruritus (19% vs 23%), increased amylase (21% vs 17%), dermatitis aciform (21% vs 17%), increased lipase (23% vs 17%), and fatigue (23% vs 8%).

Interstitial lung disease was reported in 1 patient in the PPP subset who had not received prior PD-1/PD-L1 therapy.

Of note, the label for mobocertinib includes a boxed warning for heart rate–corrected QT (QTc) prolongation including Torsade de points. Prescribers should require monitoring of QTc and electrolytes at baseline and periodically during treatment. If patients present with risk factors for QTc prolongation, increased monitoring frequency is recommended. Further, concomitant drugs known to prolong the QTc interval and the use of strong or moderate CYP3A inhibitors should be avoided. Mobocertinib should be withheld, the dose reduced, or the drug permanently discontinued based on the severity of QTc prolongation.4

For a full list of references, see the article at bit.ly/3IPcJou.
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✔ PD-L1 positive or negative status
✔ Tumors with EGFR, ALK, ROS mutations acceptable
✔ ECOG PS 0 – 1 (Fully active or able to carry out light work or activity)
✔ At least one tumor that can be safely removed by surgery for TIL and a second measurable tumor for response assessment

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CLINICALTRIALS.GOV
Lung Trial: NCT04614103
Solid tumor trial NSCLC cohorts: NCT03645928

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and effectiveness of this study has not been determined.
First-Line Durvalumab Aims to Add Additional Treatment Option in MPM

by KYLE DOHERTY

INVESTIGATORS LOOK TO BOOST systemic therapy options for patients with malignant pleural mesothelioma (MPM) with the phase 3 DREAM3R trial (NCT04334759). The study, which was initiated March 17, 2021, will further examine the safety and efficacy of durvalumab (Imfinzi) in combination with the standard chemotherapy regimen of cisplatin and pemetrexed (CP) in adult patients with MPM and attempt to fill the long unmet need for additional treatment options for this population.1

“When you block PDL-1, the idea is that the immune system can recognize foreignness within the tumor, particularly peptides and new antigens, [so that] it can then destroy the tumor cells,” explained Patrick Forde, MBBCh, director of the Thoracic Oncology Clinical Research Program and an associate professor of oncology at Johns Hopkins Medicine in Baltimore, Maryland, in an interview with OncologyLive®. “In other tumor types, including lung cancer, there has been shown to be synergy between chemotherapy and immunotherapy. Therefore, we believe that’s something [that] could potentially work well in mesothelioma as well.”

INITIAL SAFETY AND EFFICACY DATA SPARK FURTHER RESEARCH

The addition of durvalumab to CP was previously evaluated in the single-arm, phase 2 DREAM trial (ACTRN12616001170415). The trial enrolled 55 adult patients with MPM across 9 sites in Australia. Eligible patients were those with histologically confirmed MPM considered unsuitable for cancer-directed surgery, and measurable disease per modified RECIST 1.0 previously untreated with systemic therapy.2

Study participants received cisplatin 75 mg/m2, pemetrexed 500 mg/m2, and durvalumab 1125 mg intravenously on day 1 of a 3-week schedule for a maximum of 6 cycles. Treatment with durvalumab continued for up to 12 months, and safety analyses included all patients who received at least 1 dose of any study drug. The primary end point of the trial was progression-free survival (PFS) at 6 months.

Eligible patients (n = 54) were followed for a median of 28.2 months (interquartile range, 26.5-30.2) and the PFS at 6 months was 57% (95% CI, 44%-70%). The most common adverse events (AEs) of grade 3/4 were neutropenia (13%), nausea (11%), and anemia (7%). Five patients died during the study treatment, but none of these deaths was attributed to the treatment.

Investigators also evaluated the combination in patients with MPM in the single arm, phase 2 PrE0505 trial (NCT02899195). PrE0505 enrolled 55 patients across 15 sites in the United States. Patients with unresectable MPM, no prior therapies, and an ECOG performance status of 0 or 1 were eligible for the trial. Most patients had epithelioid histology (74.5%) and the median age was 68 years (range, 35-83).3

Patients were given durvalumab at a dose of 1120 mg plus pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 every 3 weeks for 6 cycles until disease stabilization or a response, then patients were given 1120 mg of durvalumab every 3 weeks until disease progression for a maximum of 1 year. The primary end point of the trial was overall survival (OS). Secondary end points included progression-free survival (PFS), objective tumor response (ORR), and adverse events (AEs). Exploratory endpoints included biomarker analysis for response in tissue and serial blood samples, PD-L1, HLA subtypes, TMB, and genomic characteristics.

End points
Primary
• OS
Secondary
• PFS
• Objective tumor response
• AEs
• HRQOL
• Health care resource use
Exploratory
• Biomarker analysis for response in tissue and serial blood samples
• PD-L1, HLA subtypes, TMB, genomic characteristics
• Validation of radiological measures of response and radiomic biomarkers

Eligibility criteria
• Adults with MPM of any histological type not amenable to curative resection
• Measurable disease per modified RECIST 1.1 for MPM
• No prior radiotherapy for measurable disease
• ECOG performance status 0 to 1
• Available tissue from diagnostic tumor biopsy
• Adequate bone marrow, kidney, and liver function
• Life expectancy ≥ 12 weeks

N = 480
2:1
n = 320
n = 160

Cisplatin* 75 mg/m2 every 3 weeks + pemetrexed 500 mg/m2 for 4 to 6 cycles
Durvalumab 1500 mg every 3 weeks + cisplatin* 75 mg/m2 every 3 weeks + pemetrexed 500 mg/m2 for 4 to 6 cycles
Durvalumab 1500 mg every 4 weeks
Observation

AEs, adverse effects; HLA, human leukocyte antigens; HRQOL, health-related quality of life; MPM, malignant pleural mesothelioma; OS, overall survival; PFS, progression-free survival; TMB, tumor mutational burden.

*Carboplatin may be used in participants who experience cisplatin-related toxicity.
Clinical Trial In Focus

MPM

specifically, the median overall survival among the 74 patients with nonepithelioid disease who received the combination was 18.1 months (95% CI, 12.2-22.8) vs 8.8 months (95% CI, 7.4-10.2) among the 75 patients treated with chemotherapy alone (HR, 0.46; 95% CI, 0.31-0.68). In the epithelioid group, the 229 patients treated with the ICI combination had a median OS of 18.7 months (95% CI, 16.9-22.0) compared with 16.5 months (95% CI, 14.9-20.5) for the 227 patients who received chemotherapy alone (HR, 0.86; 95% CI, 0.69-1.08).

“We believe there’s still a role [for nivolumab plus ipilimumab] there for treatment innovations, particularly for those patients with epithelioid disease,” Forde said. “It’s great that we have a new option for patients with MPM [with] nivolumab and ipilimumab. However, it’s notable that the benefit [with that regimen] was predominantly in those patients with nonepithelioid disease, which [accounts for] approximately 20% to 25% of patients [with MPM]. Also, survival was quite similar between chemotherapy and combination immune checkpoint therapy for patients with epithelioid MPM.”

Investigators hypothesize that the DREAM3R trial may offer a benefit for all histologies of MPM.

A SURVEY OF THE TREATMENT LANDSCAPE

Two systemic therapy options for MPM are approved by the FDA: CP and the immune checkpoint inhibitor (ICI) combination nivolumab (Opdivo) plus ipilimumab (Yervoy). The combination was approved on October 2, 2020, for the first-line treatment of adults with MPM that cannot be removed by surgery.1

“Chemotherapy was first shown to have a survival benefit for MPM [in 2003]—that was cisplatin and pemetrexed as first-line treatment for patients with newly diagnosed MPM,” Forde said. “The [median] survival in that study was 12.1 months, and that was approximately a 2- to 3-month improvement over cisplatin alone. Then for approximately 16 years, there were no advances, no new studies showing benefit. [In 2021], we saw the publication of the [results of the phase 3 CheckMate743 study] [NCT02899299], which was a global study that randomized patients to either cisplatin and pemetrexed or ipilimumab and nivolumab combination immune checkpoint therapy.”

Forde noted that the greatest survival benefit was observed in patients with nonepithelioid MPM, a histological subtype associated with poor prognosis.2 “There was a very marked benefit, improving survival from 8 months for patients with chemotherapy alone to 18 months with the [immune checkpoint combination],” he said.

Treatment will continue in the experimental arm until disease progression, unacceptable toxicity, or patient withdrawal. Tumor and quality-of-life assessments will be performed at baseline then at weeks 6, 12, 18, 26, 34, 42, and 50, followed by every 12 weeks until disease progression. A pretreatment tumor tissue sample will be required, and blood samples will be taken on day 1 of cycles 2 and 3.

To be eligible for the study, patients be at least 18 years old with MPM of any histological type that is measurable by mRECIST 1.1. Eligible patients must have an ECOG performance status of 0 or 1; adequate bone marrow, kidney, and liver function; and a life expectancy of at least 12 weeks. Patients will be recruited over a period of 27 months and followed for another 24 months.

Patients will be excluded from the trial if they have any condition requiring systemic treatment with corticosteroids or other immunosuppressive agents. Patients who received a diagnosis based on cytology or fine needle aspiration only, contraindication for immune checkpoint inhibitors, or prior systemic anticancer therapy for MPM also will be ineligible.

The primary end point of the trial is overall survival. Secondary end points include progression-free survival, objective tumor response, and safety. Exploratory objectives will include the identification of biomarkers for response in tissue and serial blood samples, such as PD-L1 expression, human leukocyte antigen subtypes, tumor mutational burden, and validation of radiological measures of response and radiomic biomarkers. The estimated study completion date is December 2025.

“Particularly for patients with epithelioid histology, we see this [phase 3 trial] as having the potential to move the paradigm further,” Forde said. “If we can demonstrate a survival benefit from adding immunotherapy up front to chemotherapy, both of which are potentially effective therapies, especially for epithelioid disease, we could have a new option in the first-line setting. That’s something we’re hopeful to find from DREAM3R and from other ongoing studies.”

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

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for the first-line treatment showed that the median OS was 20.4 months (95% CI, 13.0-28.5), which investigators noted was statistically significant compared with historical controls (P = .0014), with 70.4% (56.3%-80.7%) of patients achieving an OS of at least 12 months. The median PFS was 6.7 months; 56.4% of patients experienced a partial response and 40% had stable disease.

In terms of safety, the combination was found to be well tolerated and free of any unexpected toxicities. The most common treatment-emergent AEs (TEAEs) of any grade were fatigue (67.3%), nausea (56.4%), anemia (56.4%). Grade 3/4 TEAEs included anemia (25.5%), fatigue (7.3%), and decreased appetite (1.8%).

TREATMENT LANDSCAPE

Chemotherapy was first shown to have a survival benefit for MPM in 2003—that was cisplatin and pemetrexed as first-line treatment for patients with newly diagnosed MPM,” Forde said. “The [median] survival in that study was 12.1 months, and that was approximately a 2- to 3-month improvement over cisplatin alone. Then for approximately 16 years, there were no advances, no new studies showing benefit. [In 2021], we saw the publication of the [results of the phase 3 CheckMate743 study] [NCT02899299], which was a global study that randomized patients to either cisplatin and pemetrexed or ipilimumab and nivolumab combination immune checkpoint therapy.”

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Specifically, the median overall survival among the 74 patients with nonepithelioid disease who received the combination was 18.1 months (95% CI, 12.2-22.8) vs 8.8 months (95% CI, 7.4-10.2) among the 75 patients treated with chemotherapy alone (HR, 0.46; 95% CI, 0.31-0.68). In the epithelioid group, the 229 patients treated with the ICI combination had a median OS of 18.7 months (95% CI, 16.9-22.0) compared with 16.5 months (95% CI, 14.9-20.5) for the 227 patients who received chemotherapy alone (HR, 0.86; 95% CI, 0.69-1.08).3

“We believe there’s still a role [for nivolumab plus ipilimumab] there for treatment innovations, particularly for those patients with epithelioid disease,” Forde said. “It’s great that we have a new option for patients with MPM [with] nivolumab and ipilimumab. However, it’s notable that the benefit [with that regimen] was predominantly in those patients with nonepithelioid disease, which [accounts for] approximately 20% to 25% of patients [with MPM]. Also, survival was quite similar between chemotherapy and combination immune checkpoint therapy for patients with epithelioid MPM.”

Investigators hypothesize that the DREAM3R trial may offer a benefit for all histologies of MPM.

DETAILS OF THE DREAM3R TRIAL

DREAM3R is an open-label, randomized study that will enroll approximately 480 treatment-naïve patients with MPM in the United States, Australia, and New Zealand. Patients will be randomized 2:1 to receive durvalumab in addition to the standard treatment of CP or standard chemotherapy alone. Patients will be stratified by age (18-70 years vs older than 70 years), sex, histology (epithelioid vs nonepithelioid), and region (Australia/New Zealand vs United States).4

Patients in the experimental arm will receive durvalumab at a dose of 1500 mg every 3 weeks, plus standard cisplatin 75 mg/m² and pemetrexed 500 mg/m² every 3 weeks for 4 to 6 cycles, followed by durvalumab 1500 mg every 4 weeks. Those in the control arm will receive standard chemotherapy alone at the same dose as the experimental group for 4 to 6 cycles followed by observation (FIGURE 53).
ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status1–4

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 1,785 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, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

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 not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.
YOU RESPOND WITH ZEJULA

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS

OVERALL POPULATION (N=733)  
Reduction in the risk of 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 (n=373)  
Reduction in the risk of 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 ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to first-line platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

Important Safety Information (continued)

Allergic reactions to FD&C Yellow No. 5 (tartrazine): ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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

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


Visit ZEJULAHCP.COM to explore the PRIMA data

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Produced in USA.
Discontinuation due to thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients. [see Adverse Reactions (6)].

In PRIMA, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 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 QUADRUM, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 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 dose of ZEJULA, if necessary [see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information].

Monitor all patients treated with ZEJULA for signs and symptoms of PRES. If PRES is suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinstituting ZEJULA in patients previously experiencing PRES is not known.

Monitor 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)].

Table 2: Abnormal Laboratory Findings in ≥25% of All Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in platelet count</td>
<td>43 17 1 0</td>
<td>6 2 1 0</td>
</tr>
</tbody>
</table>
| d Includes leukopenia, lymphocyte count decreased, lymphopenia, and neutropenia (15%). Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in <1% of patients who received ZEJULA included thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 each patient).

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

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Adverse Reaction</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2</td>
<td>Headache</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased neutrophils</td>
<td>60 27 15 0</td>
<td>11 5 4 0</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51 29 7 3</td>
<td>7 3 1 0</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43 17 1 0</td>
<td>11 5 4 0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>36 23 1 0</td>
<td>11 5 4 0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>28 15 2 1</td>
<td>11 5 4 0</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>54 5 21 1</td>
<td>11 5 4 0</td>
</tr>
</tbody>
</table>
| d Includes leukopenia, lymphopenia, and neutropenia (15%). 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 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZEJULA in PRIMA Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in <2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 each patient).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in <1% of patients who received ZEJULA included thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 each patient).

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

- Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), which occurred in 3.1% of patients treated with ZEJULA in clinical trials
- MDS/AML occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 patient each).
- Permanent discontinuation due to adverse reactions occurred in 15% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%).
- Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 3: Adverse Reactions Reported in ≥1% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>46</td>
<td>23</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>40</td>
<td>32</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Acute kidney injurya</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 4: Abnormal Laboratory Findings in >25% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=179) %</th>
<th>Placebo (n=86) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Increased aspartate ammoniatransferase</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Increased alanine alamintransferase</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 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%), anemia (20%), and neutropenia (15%).

Table 5: Adverse Reactions Reported in >5% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 6: Abnormal Laboratory Findings in >25% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=179) %</th>
<th>Placebo (n=86) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

The following adverse reactions and laboratory abnormalities have been identified in ≥1% to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, and epistaxis.

Table 7: Adverse Reactions Reported in >5% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 8: Abnormal Laboratory Findings in >25% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=179) %</th>
<th>Placebo (n=86) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA. (continued on next page)
AST/ALT=Aspartate transaminase/alanine aminotransferase.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AnemiaⅠ</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>ThrombocytopeniaⅠ</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>NeutropeniaⅠ</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>0.2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83</td>
<td>26</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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.

Blood and Lymphatic System Disorders: Pancytopenia.

Immune System Disorders: Hypersensitivity (including anaphylaxis).

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES).

Psychiatric Disorders: Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).

Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

Skin and Subcutaneous Tissue Disorders: Photosensitivity.

Vascular Disorders: Hypertensive crisis.

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/or embryofetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to 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 child. Advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with ZEJULA.

Contraception

Females: 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].

8.4 Pediatric Use

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

8.5 Geriatric Use

The safety and effectiveness of ZEJULA have not been established in elderly patients.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily [see Dosage and Administration (2.4) of full prescribing information]. Niraparib exposure increased in patients with moderate hepatic impairment [total bilirubin <1.5 x upper limit of normal (ULN) to 3.0 x ULN and any aspartate transaminase (AST) level]. Monitor patients for hematologic toxicity and reduce the dose further, if needed [see Dosage and Administration (2.3) of full prescribing information]. For patients with mild hepatic impairment (total bilirubin <1.5 x ULN and any AST level or bilirubin <1.5 x ULN and AST >ULN), no dose adjustment is needed. The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST level) [see Clinical Pharmacology (12.3) of full prescribing information].

17 PATIENT COUNSELING INFORMATION

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

Melody/Drug-Induced Pseudohypothyroidism/Acute Myeloid Leukemia

Advise patients to contact their healthcare provider if they experience signs and symptoms including fever, feeling tired, weight loss, frequent infections, bruising, bleeding easily, lassitude, 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 hematological toxicity or MDS or AML, which has been reported in patients treated with ZEJULA [see Warnings and Precautions (5.1)].

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)].

Hypertension and Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first 2 months, then monthly for the first year of treatment and periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated [see Warnings and Precautions (5.3)].

Posterior Reversible Encephalopathy Syndrome

Inform patients that they are at risk of developing posterior reversible encephalopathy syndrome (PRES) that can present with signs and symptoms including seizure, headaches, altered mental status, or vision changes. Advise patients to contact their healthcare provider if they develop any of these signs or symptoms [see Warnings and Precautions (5.4)].

Dosing Instructions

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

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)].

Contraception

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

Lactation

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

Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

Advise patients that ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have aspirin hypersensitivity [see Warnings and Precautions (5.6)].

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Controlling Infections May Be Key to Improving Survival in CLL

by JASON HARRIS

Patients with chronic lymphocytic leukemia (CLL) are at an increased risk for infection no matter if they are in the pre-malignant state of monoclonal B lymphocytosis; under active surveillance, for those who are treatment-naïve; or in active treatment, said Carsten Utoft Niemann, MD, PhD, in a presentation during the 2021 Society of Hematologic Oncology Annual Meeting.1

Niemann and his colleagues hope to learn whether the natural history of immune dysfunction and infections in CLL can be better understood with the help of the machine learning-based algorithm CLL Treatment-Infection Model (CLL-TIM).

With the advent of chemoimmunotherapy and targeted therapy approaches, investigators have made great strides in improving survival for patients with CLL. Unfortunately, mortality due to infection in these patients has not changed in 4 decades, Niemann explained, and infections are now the leading cause of death among patients with CLL.

“Looking at patients who receive a diagnosis of CLL, [they] tend to have a higher risk of having a serious infection within the first 5 years,” Niemann, an associate professor, head of the CLL Lab, and chair of the Nordic CLL Study Group, Department of Hematology, at Rigshospitalet in Copenhagen, Denmark, said. “The 30-day mortality [rate of] a serious infection for patient who received a diagnosis of CLL is 10%; the 1-year mortality [rate] is only 11% for patients starting treatment for CLL even though 50% of them will have a serious infection after starting treatment. This means that infections are actually more dangerous for patients with CLL who are untreated.”

Niemann is a coinvestigator in the phase 2 PreVent-ACaLL trial (NCT03868722), in which investigators will use CLL-TIM to determine whether short-term treatment with the Bruton tyrosine kinase inhibitor acalabrutinib (Calquence) plus the BCL2 inhibitor venetoclax (Venclexta) can improve immune function and reduce the risk for infection compared with observation in patients with high-risk newly diagnosed CLL.

“The aim by this short 3-month treatment is not to cure CLL,” he said. “[Rather, the aim is to reduce the CLL clone back into what we consider monoclonal B lymphocytosis and, at the same time, treat the natural history of CLL and immune dysfunction.”

Twenty-five patients will be randomly assigned to the treatment arm, which will be given in 3 cycles of 28 days, and 25 will be assigned to observation. The primary end point is grade 3 or higher infection-free survival in the treatment arm compared with the observation arm after 24 weeks.2

CLL-TIM identifies patients at risk for infection or CLL treatment within 2 years of receiving a diagnosis as validated on both internal and external cohorts. The ensemble algorithm incorporates 28 machine learning algorithms based on data collected from 4149 patients with CLL. The model is designed to handle heterogeneous data, including high rates of missing data to be expected in the real-world setting, with a precision rate of 72% and a recall rate of 75%.3

Niemann added that 6 European nations are collaborating in the CLL-CLUE consortium to assess immune dysfunction and drug sensitivity in primary samples collected from patients and clinical trials, and biobanks. Long term, the goal is to better individualize CLL treatment.

**Immune Dysfunction Starts Long Before Diagnosis**

Niemann said that patients with CLL are more likely to be prescribed antibiotics and/or antivirals as much as 20 years before receiving a diagnosis. “This indicates that the immune dysfunction, at least, happens decades prior to diagnosis of CLL,” he added.

Niemann said looking at a patient’s entire medical history can demonstrate the burden of comorbidity in this population. “Almost all types of comorbidities for patients with CLL will increase the overall mortality and also, for most of these comorbidities, will increase the CLL-related mortality,” he said.

It appears the treatment for CLL and the disease itself play a role in incidence of infection. For example, Niemann noted that lower respiratory tract infections and urinary tract infections are common for the 6 months of treatment with ibrutinib (Imbruvica). “This may indicate that we have an improvement in immune function and lower degree of infections after the first half year on targeted therapy,” he said.

Niemann added that, outside of clinical trials, approximately 50% of patients discontinue ibrutinib by 30 months, many as a result of infections. Physicians must consider that infections may also affect the continuous treatment of patients, he said.

“On the other hand, [there is] no doubt that we may, for patients who are treated, actually improve the immune function over time,” Niemann said.

Cumulative mean numbers of infections are lower in patients whose immune globulin levels increase during ibrutinib treatment. However, Niemann said there is no clear correlation between immunoglobulin deficiency and the risk for infections.

“That is what we’ve been working on predicting the risk of infections or risk of needing treatment for CLL,” he said.

Niemann said all patients with CLL may have increased infection risk, but investigators need to identify those who at greatest risk for serious infections. Further, patients with CLL are at risk for both increased frequency of infections and also in the distribution of infections, especially for pneumococcal disease.

For a full list of references, see the article at bit.ly/3tK1XE8.
Disparities Remain as Cancer Screenings Recover From Height of COVID-19 Pandemic

by COURTNEY MARABELLA

ALTHOUGH A SUBSTANTIAL DECLINE in cancer screening tests was observed at the height of the COVID-19 pandemic, screening rates have since recovered significantly, reaching levels that exceed even pre-pandemic rates, according to Chris Labaki, MD, and Quoc-Dien Trinh, MD. However, disparities regarding these tests exist, underscoring the need for additional campaigns, outreach efforts, and resources for underserved communities.

“The recovery of cancer screening is reassuring overall, but it needs to be maintained. Larger campaigns should be implemented to ensure that we recover as many diagnoses as possible,” Labaki said. “Otherwise, patients may present with more advanced stages of the disease or may eventually receive a diagnosis at a metastatic stage, which is very unfortunate. As such, it is important to maintain this recovery and to maintain the implementation of screening tests across the nation.”

In an interview with OncologyLive®, Labaki, a postdoctoral genitourinary oncology research fellow at Dana-Farber Cancer institute, and Trinh, an associate professor of surgery at Harvard Medical School, both in Boston, Massachusetts, discussed their research.

**Q What was the rationale to conduct this research?**

**LABAKI:** [The] COVID-19 [pandemic] has been shown to affect, to a large degree, cancer screenings in the United States. Many studies have evaluated the impact of the COVID-19 pandemic on cancer screenings in many regions in the United States and have identified a large decrease in many screening types, such as prostate-specific antigen [PSA], mammography, colonoscopy, [Papanicolaou test], and even low-dose computed tomography scan, which are the most utilized screening modalities for the most common cancer types.

Our group previously published a study analyzing the impact of the pandemic on cancer screenings, as well as associated diagnosis, [and we] showed similar findings. The rationale behind [the current] study was to evaluate the impact of the pandemic on cancer screening, [particularly] between June 2020 and December 2020, [and determine] whether cancer screening tests have recovered and whether people are going for screenings again.

**TRINH:** There are 2 big [ones] with this study. We know for a fact that during the pandemic [fewer] cancer screenings were done. One the one [hand], institutions had to protect their resources such as personal protective equipment, and there was a lot of uncertainty about transmission. Institutions could not necessarily provide this service [safely at this time]. On the other [hand], patients were scared. There was concern about coming into the hospital to get testing done. Vaccines were not available at that point in time. As such, unsurprisingly but also concerningly, we found that there was a significant decrease in cancer screenings during the first wave of the pandemic. As the pandemic continued, hospitals adapted, and patients now have different expectations. They know that life continues and cancer continues. As a result, we were interested in trying to see whether cancer screenings recovered.

The other important thing we were trying to assess...[was] inequity and potential racial disparities. Often, in situations where resources are scarce, there is concern that some patients will be left behind. We wanted to know, in our large health care system, how we fared [with this]. What results would we see? Is the resumption of cancer screenings happening at the same time for everyone or are there some groups that may be more at risk? [If we noted at-risk groups,] we would need to put more energy toward getting them back to their regularly scheduled cancer screenings.

**Q Please expand on the design of the study.**

**LABAKI:** We examined a long time period on

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this study, which included 1 year before the pandemic and 9 months from the start of the pandemic. We then divided this into 7 periods, each of which was 3 months. Of the 7 periods, 4 were defined as prepandemic and 3 were [ostensibly] post pandemic. One of these would correspond with the first pandemic peak and the last period, which was from September 2020 to December 2020, would correspond with the second peak.

We evaluated patients who underwent cancer screening in the Mass General Brigham network, which is one of the largest health care systems in the northeastern United States. We evaluated the following 5 cancer screening tests: low-dose CT for lung cancer, colonoscopy for colon cancer, PSA for prostate cancer, mammography for breast cancer, and [Papanicolaou test] for cervical cancer.

We included all patients undergoing screening tests, and we also evaluated positive diagnosis tests. The goal was to look at which proportion of these tests came back positive. Finally, we evaluated the racial and socioeconomic characteristics of patients undergoing screening. The socioeconomic characteristics were evaluated using the Area Deprivation Index, which is a geocoding of a patient’s zip code. This index links the zip code of each patient to a certain degree of socioeconomic status, and it has been validated in several studies.

**What were the key findings from this research?**

**LABAKI:** Overall, we evaluated more than 380,000 patients undergoing screening across all screening types and all time periods. One of the main findings is that the number of patients undergoing screening from September 2020 to December 2020 was higher than the numbers we saw for each of the prepandemic time periods. This indicates that we had a very high recovery of cancer screening tests, as opposed to earlier time periods during the pandemic, meaning from March 2020 to June 2020, and June 2020 to September 2020, where we identified a major decrease in cancer screening tests of up to 80%. We believe that this recovery is reassuring overall; however, for colonoscopy, we did not identify a recovery. Colonoscopy was the only screening modality that did not recover to normal prepandemic levels.

When evaluating diagnosis, all screening tests and their associated positive diagnoses, [except for colonoscopy], had recovered from September 2020 to December 2020, with numbers comparable to those seen before the pandemic.

**TRINH:** These are interesting findings, and it is also somewhat expected that the recovery would not happen in the same way across all disease states. There is some expectation that certain tests are more complex than others. [For example,] the logistics of getting a colonoscopy done is much more complicated than the PSA test, which is basically just walking into an affiliated center [to get blood drawn] vs showing up to the hospital and getting a colonoscopy. Those findings are not necessarily surprising but documenting and quantifying the problem helps us understand the resources we need to dedicate to address the issue.

One important finding that we had in our study is that [we saw] some racial difference in the recovery of mammography screenings. It is an unfortunate depiction of things in the United States, and it does mean that we need to make an extra effort to ensure that underserved populations receive the care they deserve. I can say proudly that at Mass General Brigham there is a large-scale United Against Racism initiative where a lot of resources, time, and money are poured into trying to ensure that everyone gets equitable care. Some of these projects are dedicated to cancer screening, including mine, which we are leading for prostate cancer screening, as well as one dedicated to mammography and breast cancer screening. Those are exciting initiatives that arose throughout the pandemic.

**Please discuss the racial disparities revealed in this study.**

**LABAKI:** We analyzed the patient groups in each time period across each screening test, and we tried to see whether the changes we identified for cancer screening recovery or decline during the early time periods of the pandemic were impacting certain ethnic groups [to a higher degree]. For mammography, which is one of the most common screening tests with the highest numbers in our cohort, we identified racial disparities concerning the latest time period of the pandemic. We saw that non-Hispanic Black patients and Hispanic or Latino patients had a decreased proportion and decreased numbers for mammography screenings from September 2020 to December 2020. [This was in contrast] with the overall increase we identified during this time period for mammography screening.

This means that [although] mammography overall is recovering, certain ethnic populations are not experiencing this recovery. They are experiencing lower numbers compared with prepandemic time periods, which is worrisome. This underscores the need to implement large screening campaigns to include all racial groups within the population.

**TRINH:** Providing high-quality care to everyone means putting in the extra effort for certain populations that need potentially more resources. It is more than just providing equal access; it is providing more access to populations in need. A good example of that is the increasing use of telemedicine. Telemedicine certainly has played an important role in coordinating care throughout the pandemic and bringing patients back in for screening tests. However, telemedicine requires technical literacy to access Zoom platforms, to set up the call, and that is not [available] to certain populations. We need to put that extra effort in to get everyone either on board or provide them services, for example, on the telephone if they cannot set up their Zoom platform. That is also an important aspect of providing good care to everyone.

**REFERENCE**


For a detailed look at the results published in *Cancer Cell*, see the article on page 62.
Cancer Screening Tests Rebound Following First Peak of COVID-19 Pandemic

by KRISTI ROSA

AFTER A DRAMATIC DECREASE during the first peak of the COVID-19 pandemic, a substantial increase in cancer screening procedures during more recent time periods has been reported, according to data from a research letter published in Cancer Cell.

Compared with prepandemic times, defined as December 2019 to March 2020, an increase in tests performed during period 7, defined as September 4, 2020, to December 5, 2020, was noted across all types of screening analyzed, with the exception of colonoscopy. Specifically, these increases ranged from 2.0% for the Papanicolaou test to 24.0% for the prostate-specific antigen (PSA) test. In this same time period, an increase in positive diagnoses was also observed across all categories—except colonoscopy—ranging from 1.0% to 38.0%.

During period 7, the number of colonoscopy tests dropped by 15.0%, and the number of associated diagnoses also dropped by 30.0% when compared with prepandemic times. A reduction in the number of screening tests was reported during period 5 (March 2-June 2, 2020) and period 6 (June 3-September 3, 2020), respectively; this decrease ranged from 65.0% to 82.0%, respectively, and 4.0% to 44.0%, respectively.

Moreover, significant shifts were observed with regard to racial distribution of patients undergoing mammography in period 6 and period 7 vs 3 months prepandemic. Higher proportions of non-Hispanic White patients underwent mammography during these 3 time periods, at 83.2% and 82.0% vs 79.0%, respectively (P < .001). Lower proportions of non-Hispanic Black patients underwent mammography, at 5.2% and 5.3% vs 6.3%, respectively (P < .001), did Hispanic/Latino patients, at 2.4% and 2.6% vs 3.3% (P < .001).

The racial disparities were illustrated by reduced numbers of non-Hispanic Black and Hispanic patients undergoing mammography during period 7 (n = 1774 and n = 867, respectively) vs the 3 months before the pandemic (n = 1859 and n = 977, respectively); this contrasted with the increase in mammography tests in the whole group of patients analyzed. This finding was further validated by comparably significant shifts observed during periods 6 and 7 vs other prepandemic time periods.

“Although the overall increase in screening examinations is reassuring, the decrease in colonoscopy has yet to compensate,” the study authors wrote. “This highlights the importance of home-based alternatives for colon cancer screening in such particular situations. Racial disparities appear to differ between screening procedures, and they are more marked in patients undergoing mammography. Efforts to address these gaps are strongly required to ensure timely and equitable care across the patient population.”

Investigators set out to evaluate temporal changes in cancer screening tests and diagnoses in the Mass General Brigham system in Massachusetts. They also examined socioeconomic, racial, and ethnic features of patients who underwent screening during the pandemic. The COVID-19 pandemic underscored preexisting health disparities between socioeconomic and ethnic groups. However, it remains unclear whether changes in screening tests could disproportionately affect marginalized communities.

Investigators reviewed cancer screening tests and diagnoses during 7 periods of 3 months: period 1 (March 2-June 2, 2019), period 2 (June 3-September 2, 2019), period 3 (September 3-November 30, 2019), period 4 (December 1, 2019-March 2, 2020), period 5, period 6, and period 7. The first pandemic peak was during period 5 and the second peak was period 7.

Investigators looked at the following screening tests: mammography, PSA, colonoscopy, Papanicolaou test, and low-dose computed tomography (CT) scan.

To assess the impact of socioeconomic disadvantages on cancer screening, investigators used the Area Deprivation Index (ADI). A higher score translated to a greater disadvantage. To identify a patients’ national ADI, investigators used the Neighborhood Atlas. Pairwise comparisons of gender, age, race, and ADI percentiles between the time periods were calculated.

A total of 382,858 patients underwent cancer screening tests, and the mean age of these patients was 59.9 years (standard deviation, 12.3 years). Just more than half, or 58.6%, were female and the majority (80.1%) were non-Hispanic White.

After a significant decrease in screening from March 2020 to June 2020 (n = 15,453 vs n = 60,344 in period 1 vs n = 57,502 in period 2), the highest number of tests were noted during period 7 (n = 72,156), thus surpassing the number reported in the pre-pandemic period (n = 64,269). A comparable trend was showcased regarding subsequent diagnoses. When examining the different periods prior to the pandemic, periods 1 through 4, more socioeconomic disadvantage observed in those who were screened in period 5 in relation to period 4.

Additionally, a more favorable socioeconomic status was observed in patients screened in periods 6 and 7. Significant changes were noted compared with each of the 4 pre-pandemic periods. The shift in status was reported most importantly in patients who were undergoing mammography and colonoscopy.

Age variation was modest between the different time periods that were evaluated across the screening categories; the standardized mean difference ranged from 0.002 and 0.37 for all pairwise comparisons. Moreover, no difference in gender distribution was noted in colonoscopy and low-dose CT scan in the pandemic time periods vs the preceding periods.

REFERENCE

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The Multifaceted Threat of Cyberattacks in Oncology

by KYLE DOHERTY

CYBERATTACKS IN HEALTH CARE

settings are becoming increasingly prevalent—as oncologists at the University of Vermont Health Network (UVHN) learned on October 28, 2020, when a major ransomware attack infected approximately 5000 computers across the network and caused a system outage that lasted more than 40 days.

The attack caused a total loss of access to all network intranet servers, email capabilities, and clinical systems. The health network also lost access to their electronic medical record system, including laboratory, pathology, pharmacy, and radiology systems. The effect on inpatient and outpatient care delivery was profound.

“The greatest effect [of a cyberattack] is on daily clinical patient care,” Diego Adrianzen Herrera, MD, assistant professor in the Division of Hematology and Oncology at the Larner College of Medicine and a member of the University of Vermont Medical Center in Burlington, said. “A lot of the systems that we use in oncology are dependent on checks and balances from a multidisciplinary team, including pharmacy and specialty nursing, which are automated in the electronic medical record. When we lost access to that, the biggest immediate [effect] was the inability to communicate across interdisciplinary teams to safely provide treatments to patients.” Herrera said that prior to the attack outside the electronic medical record, there was little communication between systems.

Following resolution of the incident, investigators at the University of Vermont Medical Center published a paper, which Herrera coauthored, outlining the key takeaways from their experience. The report detailed the response to the ransomware attack and provided steps that both community and academic-based practices can take to lessen the effect on patient care should they experience a cyberattack (FIGURE 1).

“What the most important lesson we learned from what happened to us was to have a backup, even if that means going backward and doing everything in a secure manner by paper,” Herrera said. “Patient care will be immediately affected more than anything else.”

WHAT DELAYS IN CARE LOOK LIKE

System-level delays have been documented to have a direct effect on patient outcomes, according to results of a meta-analysis. Investigators conducted a systemic review of 34 studies that included 17 cancer treatment indications and more than 1 million participants to determine trends in patient survival according to wait time for treatment, including surgery, systemic treatment, or radiotherapy. 1

The delay was significantly increased mortality in 13 of the 17 indications (P < .05). HRs for overall survival were estimated for each 4-week delay in cancer care, representing the risk of death for patients who experienced observed treatment delays compared with those who did not experience a delay. Surgical delays were consistently associated with increased mortality, with an HR range between 1.06 and 1.08—translating to a 6% to 8% increased chance of death for each 4-week delay. Delays in adjuvant and neoadjuvant treatments had an HR range of 1.01 to 1.28. Investigators reported that high-validity data were limited for curative radiotherapy; however, significant effects of delays were reported for patients with head and neck cancers (HR, 1.09; HR range, 1.05-1.14) and those with cervical cancer (HR, 1.23; HR range, 1.00-1.50). 2

The investigators concluded that policies that focus on minimizing system-level delays (such as those generated in the fallout of a cyberattack) would maintain or improve population-level survival outcomes. 2 Due to the increasing frequency of cyberattacks along with the transition to electronic-based forms of filing and communication, multiple facets of oncology operations should be preemptively addressed to ensure preparedness to maintain continuous, safe care of patients.

ADDRESSING COMMUNICATION CHALLENGES

The cyberattacks caused both the wired and wireless internet networks of UVHN to go completely offline, with no access to the email server. Only a single fax machine was left operational. In addition to internal communications being severed, external communication with patients was also severely hampered because the centralized call center for incoming patients was unable to quickly relay messages to the clinic offices and because outreach was made impossible since patient contact information was stored in the electronic medical record.

“The major problem we ran into in the midst of everything happening was that some people were text and emailing [using] personal accounts. Initially there was a lot of chaos,” Herrera said.

In response to the communication challenges caused by the ransomware attack, UVHN had to quickly implement alternate communication methods. First, the institution worked to establish SMS text groups to coordinate secure videoconferencing sessions to facilitate interprofessional communication. Participants in the video conferences were meticulously identified to avoid potential intrusion by hackers.

The university was forced to rely on the regional health information exchange to attempt to access patient information, as well as third-party internet-based services for contact information. Although clinical summaries, demographics, and laboratory results were accessible, it was largely insufficient because of the requirement of individual provider registration.

Considering the communication challenges faced during the attack, UVHN
suggested several potential improvements and contingency plans for their communication procedures. These included ensuring cell phone coverage in the hospital and clinics, maintaining an offline database of patient information, and establishing group texts between key caregivers and administrators. “The key is having standardized communications strategies in place outside of whatever is your norm,” Herrera said.

Timely and transparent communication presented a challenge for the University of Vermont Health Network. As mentioned, potential improvements and contingency plans for their communication procedures were proposed and included establishing an emergency cell phone system in the hospital and clinics, maintaining an offline or alternative server database of patient information, and establishing a centralized triaging system for rerouting patient care with partner services.

“If there’s one thing that people can prepare for, it’s to have a plan for communication across the different members of the team,” Herrera said. “Another major factor to think about is establishing leaders. We were fortunate in that everyone wanted to help, but we learned that if we can clarify who will take care of which part of care, it’s more productive than everyone trying to do everything for their patients by themselves.”

PROVIDING ONCOLOGIC CARE IN THE WAKE OF A CYBERATTACK

With limited pathways for clear communication among interdisciplinary care teams and no electronic safeguards in place for multistep care regimens, UVHN needed to establish protocols to ensure that patients could be safely treated in the wake of the mass outage.

The loss of access to the electronic medical records and schedules at UVHN resulted in a 41% reduction in the delivery of clinical outpatient care, a 52% drop in infusion visit volume, and the need for the system to establish command centers to restore services for new patients, including triaging diagnostic evaluation, delivering therapies, and addressing referrals. The oncology-specific services most affected included access to chemotherapy plan templates, which communicated nursing and pharmaceutical processes for systemic care delivery, as well as electronic safeguards leveraged during treatments that required multiple steps in both preparation and delivery.

Several areas of need should be included when determining measures for offline and secure protocols including, but not limited to, the needs of those requiring inpatient systemic therapy, outpatient infusions, radiology imaging, and other diagnostic and continued care measures.

One example from the UVM study regarded administration of inpatient chemotherapy. All treatment plans stored in the electronic records—which included dose modifications, contact information, at-home medication information, pathology results, and more—were inaccessible. In response, all chemotherapy orders were rewritten by the primary oncologist, and patients were asked to carry with them any medications and available medical records. Chemotherapy plans were submitted for review at least a day in advance, and the primary oncologist decided on dose modifications based on the available information.

### FIGURE. Preparative Measures to Address Future Cyberattack Challenges

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>PROPOSED PREPARATION</th>
</tr>
</thead>
</table>
| Loss of secure communication platforms | • Create an emergency cell phone system for all hospital services  
• Backup overhead paging system  
• Maintain an alternative secure message services |
| Loss of access to patient data | • Create and active, updated patient roster with medical record number, date of birth, contact information, and insurance on a separate server  
• Nonelectronic protocols should be created or updated and readily available for activation with buy-in from all stakeholders  
• Rapid availability of comprehensive paper orders |
| Lack of electronic safeguards in multilevel therapeutic delivery | • Establish protocol for centralized triaging of actively treated patients and communication with patients  
• Establish capabilities of partner hospitals to care for patients with cancer |
| Inability to provide systemic therapy to the usual volume of patients with scheduled visits | • Establish protocols for patients to undergo necessary testing at partner sites and create awareness of unique challenges this population faces |
| Inability to work up and treat patients who receive a new diagnosis of cancer | • Create awareness of challenges that will arise with the loss of older films for comparison and inability to access local imaging where clinical decisions hinge on availability of cross-sectional imaging |
| Loss of access to outpatient imaging studies | • Establish consensus-based plan or options for documentation of clinical and infusion visits during downtime  
• Availability of paper billing sheets  
• Availability of phone dictation or other noncomputer-based options for documentation |
| Loss of electronic platforms for documentation and billing | • |
A set of chemotherapy templates for frequently used protocols was assembled for use for incoming patients. The entirety of each chemotherapy regimen, including premedications and emergency plans, was manually recorded and stored prior to administration. The investigators recommend the creation of backup patient files stored on an alternative server or in paper form. Additionally, nonelectronic protocols, with buy-in from all stakeholders, should be created and include a centralized tirage method for all actively treated patients.

For example, a UVHN transdisciplinary team of nurse navigators in conjunction with oncologists in the new patient command center evaluated and screened new or recent cancer diagnosis referrals based on cancer type. Patients were separated into 2 groups: recently established patients and new referrals. Special populations included neuro-oncology and cognitively impaired populations, patients scheduled to undergo autologous stem cell transplant, and patients involved in research studies.

A written list of recently evaluated patients was created by intake coordinators, and a treating physician was identified for each case. The needs of each case were communicated by the treating physician, with priority placed on the expedited completion of diagnosis and staging and the timely initiation of treatment. The outpatient command center was then tasked with coordinating diagnostic biopsies, genetic testing, and radiographic scans.

Easily verifiable regimens including continuous infusions, frequent treatments, and fixed-dose regimens were identified. The capability for triple verification of infusion details with verification of treatment plans by a pharmacist according to the cancer diagnosis and national guidelines was also required. Investigators at UVHN also recommend having paper copies of the most up-to-date versions of commonly used chemotherapy protocols, including the National Comprehensive Cancer Network guidelines, on file.

If the criteria were met, written orders were provided a day in advance by the treating physician for verification by nurses and pharmacy staff. All other patients were screened by a command center. Delays in the laboratory necessitated the completion of blood work 24 to 48 hours before chemotherapy and the utilization of outside facilities in some cases.

Command centers handling outpatient care, inpatient care, radiology challenges, and new patients were established soon after the institution realized that the disruption could continue for an extended period of time.

The outpatient command center was able to create a paper database of patient information for all patients receiving treatment during the system downtime. Patients with missed or upcoming therapy were stratified by physicians into tier 1 (curative intent, urgent/lifesaving, need for highly symptomatic disease, and proven survival advantage), tier 2 (safe to delay 1-2 weeks), and tier 3 (safe to delay at least 2 weeks).

New patient care proved to be a hurdle in the wake of the attack. Patients were stratified into 2 groups: those who were recently established and those who were new referrals. A primary care provider was assigned to recently established patients and triaged the expedited completion of their diagnosis and initiation of treatment. From there, these patients were referred to the outpatient command center for any further testing and coordination of procedures.

“The other group [that was particularly affected by the attack] were the new patients,” Herrera noted. “We are a big center and the only referral center for a very large population. [We’re also] the only center that can do certain specific testing, such as genetic testing and molecular panels. Work-up for a new diagnosis was definitely delayed. Even if the clinician came up with algorithms to solve [the problem], the lab was still down, and they just couldn’t function at the speed at which we would like for these specialty tests.”

New referrals were only taken on if urgent—for example those with acute leukemia—and were prioritized for admission and work-up; other nonurgent referrals were routed to community or network sites, once again relying on the preestablished open lines of communication between centers.

“[These attacks] are becoming so frequent,” Herrera said. “Every large health care network at this point should have backup systems and plans prepared for a potential cyberattack that blocks all of their communications. I hope [that this creates] awareness that this is just becoming the norm.

“There were 400 cyberattacks [targeting] health care facilities in the United States last year alone. The biggest takeaway is that these types of attacks are only going to get more and more common.”
OncLive On Air™ is a podcast from OncLive®, which provides oncology professionals with the resources and information they need to provide the best patient care. In both digital and print formats, OncLive® covers every angle of oncology practice, from new technology to treatment advances to important regulatory decisions.

In our exclusive interview, Toni K. Choueiri, MD, provides perspectives on the FDA approval of nivolumab and cabozantinib in advanced renal cell carcinoma.
A Dynamic Treatment Landscape Emerges for Early-Stage TNBC

by ERIN ROESCH, MD

TRIPLE-NEGATIVE BREAST CANCER (TNBC) is a biologically complex subtype characterized by an aggressive nature and heterogeneity. Standard chemotherapy has historically been the mainstay of treatment for patients with diagnoses of early-stage TNBC, but there remains an unmet need to identify novel therapies that improve outcomes and, equally important, to discern which patients may benefit from a given treatment.

IMMUNOTHERAPY
The anti–PD-1 monoclonal antibody pembrolizumab (Keytruda) has shown impressive antitumor activity in the metastatic and curative settings for patients with TNBC. In the phase 3 KEYNOTE-355 trial (NCT02819518), the addition of pembrolizumab to chemotherapy significantly improved progression-free survival (PFS) vs chemotherapy alone among patients with previously untreated locally advanced inoperable TNBC and combined positive score of at least 10. Specifically, the median PFS was 9.7 months with pembrolizumab/chemotherapy vs 5.6 months with placebo/chemotherapy (HR, 0.65; 95% CI, 0.49-0.86; P = .0012).1

In the curative space, neoadjuvant systemic therapy is favored for patients with early TNBC—specifically for tumors that are larger than 2 cm or with nodal involvement—and may be considered for smaller tumors in certain cases. Potential benefits of neoadjuvant chemotherapy include goal of downstaging the primary tumor and/or axilla to allow more surgical options (ie, breast-conserving surgery vs mastectomy) and assessment of the biology of the cancer via chemotherapy response, which can have prognostic and therapeutic implications. In I-SPY2 (NCT01042379), a phase 2 adaptively randomized platform trial for high-risk, stage II/III breast cancer evaluating multiple investigational arms in different subtypes in parallel fashion, the addition of pembrolizumab to neoadjuvant chemotherapy (taxane-based and anthracycline-based) more than doubled the pathologic complete response (pCR) rate in hormone receptor–positive/HER2-negative and triple-negative subtypes.2

Investigators of the phase 3 KEYNOTE-522 trial (NCT03036488) evaluated the role of pembrolizumab added to chemotherapy for high-risk (stage II/III) TNBC in the neoadjuvant setting. The chemotherapy backbone consisted of paclitaxel/carboplatin followed by anthracycline (doxorubicin or epirubicin)/cyclophosphamide. After surgery, patients received adjuvant pembrolizumab (n = 784) or placebo (n = 390) every 3 weeks for up to 9 cycles. The pCR rate was 64.8% in the pembrolizumab/chemotherapy group vs 51.2% in the placebo/chemotherapy group, yielding an absolute benefit of 13.6% (95% CI, 5.4-21.8; P < .001).3 Notably, pembrolizumab benefit was seen irrespective of PD-L1 status.

OLAPARIB PROVES EFFECTIVE IN MUTANT DISEASE
Breast cancers associated with BRCA4 mutations are more prone to double-strand DNA breaks that cannot be repaired because of a defective homologous recombination repair pathway. PARP inhibition leads to synthetic lethality and cancer cell apoptosis. Two PARP inhibitors, olaparib (Lynparza) and talazoparib (Talzenna), have demonstrated PFS benefit compared with chemotherapy in patients with germline BRCA4 mutations and HER2-negative metastatic breast cancer, in the OlympiAD (NCT02000622) and EMBRACA (NCT01945775) trials, respectively.5,6

The phase 3 OlympiA trial (NCT02032823) was designed to explore the role of olaparib in the adjuvant setting among patients with HER2-negative early breast cancer with BRCA4 germline mutations after receipt of neoadjuvant or adjuvant chemotherapy. Patients with TNBC were required to have a primary tumor measuring at least 2 cm or node-positive disease if treated in the adjuvant setting, or presence of residual disease (no pCR) post neoadjuvant chemotherapy.

One year of adjuvant olaparib led to a statistically significant improvement in both invasive and distant disease-free survival (DFS), with absolute benefits of 8.8% and 7.1%, respectively (TABLE). The 3-year invasive DFS rate was 85.9% in the olaparib group vs 77.1% in the placebo group (HR, 0.58; 95% CI, 0.41-0.82; P < .001).
The 3-year distant DFS rate was 87.5% in the olaparib group vs 80.4% in the placebo group (HR, 0.57; 95% CI, 0.39-0.83; P < .001).7

### RESIDUAL DISEASE POST NEOADJUVANT THERAPY

The presence of increasing amounts of residual disease after neoadjuvant systemic therapy has been shown to correlate with inferior prognosis compared with those patients who achieve a pCR or have minimal residual cancer burden (RCB). Symmans et al investigated long-term prognosis in each breast cancer phenotype related to RCB post neoadjuvant chemotherapy.ª Among those with TNBC, good prognoses were seen for patients who achieved a pCR or RCB-I; outcomes were inferior for those with RCB-II or RCB-III (estimated 5-year relapse-free survival rates: pCR 94%, RCB-I 89%, RCB-II 62%, RCB-III 26%).ª Thus, efforts have been focused on developing strategies to improve outcomes for patients who have a less robust response to neoadjuvant therapy.

In the phase 3 CREATE-X trial (UMIN000000843), patients with HER2-negative breast cancer with residual disease after neoadjuvant chemotherapy (anthracycline, taxane, or both) were randomized to capecitabine for 6 to 8 cycles, or standard postsurgical management (control group). This study demonstrated DFS and OS benefit with the addition of capecitabine vs control in the TNBC subgroup. The 5-year DFS rates were 69.8% vs 56.1%, respectively (HR, 0.58); the 5-year OS rates were 78.8% vs 70.3%, respectively (HR, 0.52).ª As a result, adjuvant capecitabine became standard of care for patients with residual TNBC post neoadjuvant therapy.

The phase 3 ECOG-ACRIN EA1131 trial (NCT02445391) randomized 410 patients with stage I/II TNBC who had at least 1 cm of residual disease after completion of neoadjuvant chemotherapy (taxane with or without anthracycline) to platinum-based chemotherapy or capecitabine. After a median follow-up of 20 months, the 3-year invasive DFS rates were 42% with platinum and 49% with capecitabine (HR, 1.06) for patients with basal subtype TNBC. Furthermore, grade 3/4 toxicities were higher in the platinum arm.ª This trial was therefore stopped early because of the improbability of demonstrating noninferiority.

### NEW INDICATIONS, NEW QUESTIONS

The treatment of early-stage TNBC is evolving rapidly. Although these advances provide additional options for patients, they simultaneously create more questions for oncologists. Considerations include selection of patients for various therapies, how to sequence agents, and monitoring of adverse effects. As more experience is gained with these treatments and guidelines build on data and approvals, questions will gradually be answered, although new ones surely will arise as the early TNBC field continues to expand.

**REFERENCES**


IN THE TREATMENT OF METASTATIC EGFRm NSCLC

FIRST-LINE TAGRISSO: TO FIND EVERY ELIGIBLE PATIENT TEST, KNOW, TREAT

GIVE ELIGIBLE PATIENTS A CHANCE AT GROUNDBREAKING EFFICACY

<table>
<thead>
<tr>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.9 vs 10.2 months for TAGRISSO vs erlotinib/gefitinib¹</td>
<td>38.6 vs 31.8 months for TAGRISSO vs erlotinib/gefitinib¹</td>
</tr>
<tr>
<td>HR=0.46 (95% CI: 0.37, 0.57), P=0.0001</td>
<td>HR=0.80% (95% CI: 0.64, 1.00), P=0.0462</td>
</tr>
</tbody>
</table>

FLAURA study design: Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR-TKI comparator arm (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. crossover was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included OS, ORR, CNS PFS, and DoR. To provide strong control for the type I error rate, the primary endpoint of PFS and endpoints of OS and CNS PFS were tested sequentially.¹⁻⁴

INDICATION

- TAGRISSO is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTC) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a QTC >500 msec, and 3.1% of patients had an increase from baseline QTC >60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study (1.5% [5/325] of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%). Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist

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FOR ALL NEWLY DIAGNOSED METASTATIC NSCLC PATIENTS, ENSURE YOU:

1. **TEST** all metastatic NSCLC patients for EGFRm and other actionable mutations
2. **KNOW** your patients’ full molecular results before initiating treatment
3. **TREAT** metastatic EGFRm NSCLC patients with first-line TAGRISSO

Learn more at TagrissoTKT.com

**IMPORTANT SAFETY INFORMATION (CONT’D)**

- Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.
- Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.
- Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough.

TARGRISSO® (osimertinib) tablets, for oral use
Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)
TARGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC
TARGRISSO is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC
TARGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1) in the full Prescribing Information].

DOSAGE AND ADMINISTRATION
Patient Selection
Select patients with resectable tumors for the adjuvant treatment of NSCLC with TARGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens [see Clinical Studies (14) in the full Prescribing Information]. Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TARGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens [see Clinical Studies (14) in the full Prescribing Information]. Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, test tumor tissue if feasible.

Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with TARGRISSO following progression on or after EGFR TK therapy based on the presence of an EGFR T790M mutation in tumor or plasma specimens [see Clinical Studies (14) in the full Prescribing Information]. Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen
The recommended dosage of TARGRISSO is 80 mg tablet once a day. TARGRISSO can be taken with or without food.

If a dose of TARGRISSO is missed, do not make up the missed dose and take the next dose as scheduled. Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity or for up to 5 years.

Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.

Administration to Patients Who Have Difficultly Swallowing Solids
Disperse tablet in 60 mL (2 ounces) of non-carbonated water. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink. If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 50 mL).

Dosage Modifications

Table 1. Recommended Dosage Modifications for TARGRISSO

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary [see Warnings and Precautions (5.2, 5.3) in the full Prescribing Information]</td>
<td>Interstitial lung disease (ILD)/Pneumonitis</td>
<td>Permanently discontinue TARGRISSO.</td>
</tr>
</tbody>
</table>

Adverse Reactions

Table 1. Recommended Dosage Modifications for TARGRISSO (cont’d)

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac [see Warnings and Precautions (5.1) in the full Prescribing Information]</td>
<td>QTc interval greater than 500 msec on at least 2 separate ECGs</td>
<td>Withheld TARGRISSO until QTc interval is less than 481 msec or recovery to baseline if QTc is greater than or equal to 481 msec, then resume at 40 mg dose.</td>
</tr>
<tr>
<td>QTc interval prolongation with signs/symptoms of life-threatening arrhythmia</td>
<td>Permanently discontinue TARGRISSO.</td>
<td></td>
</tr>
<tr>
<td>Symptomatic congestive heart failure</td>
<td>Permanently discontinue TARGRISSO.</td>
<td></td>
</tr>
<tr>
<td>Cutaneous [see Warnings and Precautions (5.5) in the full Prescribing Information]</td>
<td>Stevens-Johnson syndrome (SJS), Erythema Multiforme Major (EMM)</td>
<td>Withheld TARGRISSO if suspected and permanently discontinue if confirmed.</td>
</tr>
<tr>
<td>Other [see Adverse Reactions (6.1) in the full Prescribing Information]</td>
<td>Adverse reaction of Grade 3 or greater severity</td>
<td>Withheld TARGRISSO for up to 3 weeks.</td>
</tr>
<tr>
<td>Improvement to Grade 0-2 within 3 weeks</td>
<td>Resumes at 80 mg or 40 mg daily.</td>
<td></td>
</tr>
<tr>
<td>No improvement</td>
<td>Permanently discontinue TARGRISSO.</td>
<td></td>
</tr>
</tbody>
</table>

ADVERSE REACTIONS

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

- Interstitial Lung Disease/Pneumonitis [see Warnings and Precautions (5.1) in the full Prescribing Information]
- QTc Interval Prolongation [see Warnings and Precautions (5.2) in the full Prescribing Information]
- Cardiomyopathy [see Warnings and Precautions (5.3) in the full Prescribing Information]
- Keratitis [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Erythema multiforme and Stevens-Johnson syndrome [see Warnings and Precautions (5.5) in the full Prescribing Information]
- Cutaneous Vasculitis [see Warnings and Precautions (5.6) in the full Prescribing Information]

Clinical Trials Experience

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

The data in the Warnings and Precautions section reflect exposure to TARGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TARGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials (ADAURA [n=337], FLAURA [n=270], and AURA3 [n=279]), two single arm trials (AURA Extension [n=201] and AURA2 [n=210]), and one dose-finding study, AURA1 (n=173) [see Warnings and Precautions (5) in the full Prescribing Information]. Among 1479 patients who received TARGRISSO, 81% were exposed for 6 months or longer and 60% were exposed for greater than one year. In this pooled safety analysis, the most common adverse reactions in ≥20% of 1479 patients who received TARGRISSO were diarrhea (47%), rash (45%), musculoskeletal pain (36%), nail toxicity (33%), dry skin (32%), stomatitis (28%), fatigue (21%), and cough (20%). The most common laboratory abnormalities in ≥30% of 1479 patients who received TARGRISSO were leukopenia (65%), lymphopenia (62%), neutropenia (57%), anemia (47%), and neutrophilia (36%).

The data described below reflect exposure to TARGRISSO (80 mg daily) in 337 patients with EGFR mutation-positive resectable NSCLC and 568 patients with EGFR mutation-positive metastatic NSCLC in three randomized, controlled trials (ADAURA [n=337], FLAURA [n=279], and AURA3 [n=279]). Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrolment in these studies. Keratitis

Keratitis was reported in 0.7% of 1479 patients treated with TARGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye irritation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

Erythema Multiforme and Stevens-Johnson Syndrome

Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TARGRISSO. Withholding TARGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

Cutaneous Vasculitis

Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and tumor vasculitis have been reported in patients receiving TARGRISSO. Withholding TARGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TARGRISSO based on severity.

Embry-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TARGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, somitomerria was post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When treated with TARGRISSO and then treated with untreated females, there was an increase in prepartum embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Various measures of female reproductive potential prior to initiating TARGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TARGRISSO for at least 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose [see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information].
Adverse Reactions in FLAURA* (cont’d)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PLACEBO (N=337)</th>
<th>TAGRISSO (N=279)</th>
<th>All Grades (N=616)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 or higher (%)</td>
<td>Grade 4 (%)</td>
<td>Grade 3 or higher (%)</td>
</tr>
<tr>
<td><strong>Laboratory Abnormalities</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hematology</td>
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</tr>
<tr>
<td>Anemia</td>
<td>30 0.9 12 0.3 42 1.3</td>
<td>26 0.9 7 0.2 33 1.2</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>20 0.6 10 0.3 30 0.9</td>
<td>18 0.6 7 0.2 25 0.8</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25 2.2 10 0.3 35 1.1</td>
<td>25 2.2 10 0.3 35 1.1</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>23 0.7 7 0.2 30 0.9</td>
<td>23 0.7 7 0.2 30 0.9</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA**

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. Serious adverse reactions were reported in 4% of patients treated with TAGRISSO, the most common serious adverse reactions (≥1%) were pneumonia (2.9%), 9/15/21   11:56 AM

The safety of TAGRISSO was evaluated in ADAURA, a randomized, double-blind, placebo-controlled trial for the adjuvant treatment of patients with EGF receptor exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection with or without prior adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 25.5 months. Serious adverse reactions were reported in 16% of patients treated with TAGRISSO. The most common serious adverse reaction (≥1%) was pneumonia (1.5%). Adverse reactions leading to dose reductions or interruptions occurred in 9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were diarrhea (4.5%), stomatitis (3.9%), nail toxicity (1.8%) and rash (1.8%). Adverse reactions leading to permanent discontinuation occurred in 11% of patients treated with TAGRISSO. The most frequent adverse reactions leading to discontinuation of TAGRISSO were interstitial lung disease (2.7%), and rash (1.2%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in ADAURA.

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in ADAURA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PLACEBO (N=337)</th>
<th>TAGRISSO (N=279)</th>
<th>All Grades (N=616)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 or higher (%)</td>
<td>Grade 4 (%)</td>
<td>Grade 3 or higher (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>47 2.4 20 0.6 67 2.0</td>
<td>50 2.4 25 0.8 75 2.6</td>
<td></td>
</tr>
<tr>
<td>Stomatitis‡</td>
<td>32 1.8 7 0.2 39 1.2</td>
<td>34 1.8 7 0.2 41 1.3</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain**</td>
<td>12 0.3 7 0.2 19 0.6</td>
<td>12 0.3 7 0.2 19 0.6</td>
<td></td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash§</td>
<td>40 0.6 19 0.6 59 1.8</td>
<td>40 0.6 19 0.6 59 1.8</td>
<td></td>
</tr>
<tr>
<td>Nail toxicity§</td>
<td>37 0.9 3.8 0.4 45 1.4</td>
<td>37 0.9 3.8 0.4 45 1.4</td>
<td></td>
</tr>
<tr>
<td>Dry skin¶</td>
<td>29 0.3 7 0.2 36 1.1</td>
<td>29 0.3 7 0.2 36 1.1</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 0 9 0.3 28 0.9</td>
<td>19 0 9 0.3 28 0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19 0 9 0.3 28 0.9</td>
<td>19 0 9 0.3 28 0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous Pain</td>
<td>18 0.3 25 0.7 36 1.1</td>
<td>18 0.3 25 0.7 36 1.1</td>
<td></td>
</tr>
<tr>
<td><strong>Infection and Infestation Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 0 10 0.3 24 0.7</td>
<td>14 0 10 0.3 24 0.7</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 0.6 10 0.3 23 0.7</td>
<td>13 0.6 10 0.3 23 0.7</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 0.3 7 0.2 17 0.5</td>
<td>10 0.3 7 0.2 17 0.5</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>13 0.6 9 0.3 22 0.7</td>
<td>13 0.6 9 0.3 22 0.7</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness**</td>
<td>10 0 9 0.3 19 0.6</td>
<td>10 0 9 0.3 19 0.6</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 0.6 3.6 0.9</td>
<td>13 0.6 3.6 0.9</td>
<td></td>
</tr>
</tbody>
</table>

* Includes dry skin, skin fissures, xerosis, and pruritus.
† One grade 5 (fatal) event was reported (<0.1%) for EGFR TKI comparator.
‡ Includes stomatitis and mouth ulceration.
§ Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash purpuric, rash pruritic, rash vesicular, rash follicular, erythema, telangiectasia, acne, dermatitis, dermatitis acrodermatitis, dry eruption, skin erosion, pruritus.
¶ Includes dry skin, skin fissures, xerosis, and pruritus.
† Includes fatigue, anemia.
§ Includes dry skin, skin fissures, xerosis, xeroderma.
‖ Includes nail bed disorder, nail bed inflammation, nail bed ulceration, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onycholysis, onychodystrophy, onychophagia, onychomadesis, onychoschizia, posthonychus.
§§ Includes pruritus, pruritus generalized, eyelash pruritus.
∫ Includes fatigue, anemia.
∫ Includes dry skin, skin fissures, xerosis, and pruritus.
‡ Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268.
† One grade 5 (fatal) event was reported (<0.1%) for EGFR TKI comparator.
§ Includes dry skin, skin fissures, xerosis, xeroderma.
¶ Includes nail bed disorder, nail bed inflammation, nail bed ulceration, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychalgia, onycholysis, onychodystrophy, onychophagia, onychomadesis, onychoschizia, posthonychus.
∫ Includes fatigue, anemia.
∫ Includes dry skin, skin fissures, xerosis, xeroderma.
‡ Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO range: 179 and EGFR comparator (191).
chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 (35%), female (64%), Asian (65%), never smokers (68%), and EGFR PS 0 or 1 (100%). Serious adverse reactions were reported in 16% of patients treated with TAGRISSO and 28% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (LDL-pseudoplasmas). Dose reductions occurred in 29% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (2%). Tables 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3.

### Table 6. Adverse Reactions Occurring in >10% of Patients Receiving TAGRISSO in AURA3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy/Pemetrex/Cisplatin (N=136)</th>
<th>All Grades (%)</th>
<th>Grade 3/4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41</td>
<td>1.1</td>
<td>11</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>0.7</td>
<td>49</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>19</td>
<td>0.7</td>
<td>49</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0.4</td>
<td>20</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>34</td>
<td>1.2</td>
<td>6</td>
<td>0.2</td>
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<tr>
<td>Dry skin</td>
<td>23</td>
<td>0.9</td>
<td>2</td>
<td>0.1</td>
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<td></td>
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<tr>
<td>Nail toxicity</td>
<td>22</td>
<td>0.8</td>
<td>1</td>
<td>0.1</td>
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<td></td>
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<tr>
<td>Pruritus</td>
<td>13</td>
<td>0.5</td>
<td>2</td>
<td>0.1</td>
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<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18</td>
<td>0.6</td>
<td>36</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>0.6</td>
<td>14</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
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<td></td>
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<tr>
<td>Back pain</td>
<td>10</td>
<td>0.4</td>
<td>4</td>
<td>0.1</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
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<tr>
<td>Decreased weight</td>
<td>11</td>
<td>0.4</td>
<td>3</td>
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<tr>
<td>Gynecological Disorders</td>
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<tr>
<td>Dysmenorrhea</td>
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<td>2</td>
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</tr>
<tr>
<td>Hematologic Disorders</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43</td>
<td>1.5</td>
<td>79</td>
<td>3.1</td>
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</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>8</td>
<td>61</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46</td>
<td>1.6</td>
<td>48</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27</td>
<td>2.2</td>
<td>49</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 7. Laboratory Abnormalities Worsening from Baseline in >20% of Patients in AURAX

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy/Pemetrex/Cisplatin (N=136)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43</td>
<td>0</td>
<td>79</td>
<td>3.1</td>
<td></td>
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</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>8</td>
<td>61</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46</td>
<td>0.7</td>
<td>48</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27</td>
<td>2.2</td>
<td>49</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
<td>0.4</td>
<td>18</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>26</td>
<td>3.7</td>
<td>36</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>22</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td>Hyperkalemia</td>
<td>9</td>
<td>1.4</td>
<td>13</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No dose adjustment is recommended in patients with creatinine clearance (CrCl) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CrCl ≤15 mL/min) [see Clinical Pharmacology (12.3) in the full Prescribing Information].
**TP53** and **IGHV** Status Retain Utility as Prognostic Markers in CLL

by JESSICA HERGERT

**HISTORICAL PROGNOSTIC MARKERS FOR** chemoimmunotherapy have largely lost their clinical relevance in the context of targeted therapies for patients with chronic lymphocytic leukemia (CLL); however, **IGHV** and **TP53** mutational status remain important predictive markers of response, now for novel treatments, according to a debate that took place during the 2021 Society of Hematologic Oncology Annual Meeting.1,2

Although several markers of CLL activity and growth—notably **IGHV** and **TP53** mutational status—are predictive of outcomes with fludarabine, cyclophosphamide, and rituximab (FCR; Rituxan), the advent of targeted therapy has largely replaced chemoimmunotherapy as a treatment option for patients with CLL. Therefore some debate exists regarding the current utility of these markers in patients receiving continuous therapy with Bruton tyrosine kinase (BTK) inhibitors or time-limited therapy with venetoclax (Venclexta).

During the debate, Inhye Ahn, MD, a clinical fellow at the National Heart, Lung, and Blood Institute at the National Institutes of Health in Bethesda, Maryland, spoke in favor of using old prognostic markers in CLL. Taking the opposing side, Steven Coutre, MD, a professor of medicine at Stanford University in California, argued against using old prognostic markers.

Following both presentations, 89% of audience members voted in favor of using old prognostic markers in CLL management, according to a virtual poll.

Both presenters concluded that although the prognostic vs predictive value of **IGHV** and **TP53** mutational status remains uncertain, all patients with CLL in clinical practice or enrolled in clinical trials should undergo fluorescence in situ hybridization (FISH) testing, as well as **TP53** and **IGHV** mutational analysis. These conclusions are corroborated by the International Workshop on CLL (iwCLL) guidelines for the diagnosis, treatment indications, response assessment, and supportive management of CLL (Table).3

**IGHV MUTATIONS**

Somatic hypermutation of **IGHV** is a stable marker in CLL, with unmutated **IGHV** predicting unfavorable response to chemoimmunotherapy. However, in the context of targeted agents, no difference in progression-free survival (PFS) was observed between patients with mutated **IGHV** or unmutated **IGHV** who were treated with ibrutinib (Imbruvica).4 Additionally, no difference in PFS was observed between **IGHV** mutational status in patients treated with venetoclax/obinutuzumab (Gazyva).5

**TABLE.** iwCLL Recommendations for Patients with CLL

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>General practice</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test to establish diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Immunophenotyping of peripheral blood lymphocytes</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Assessment before treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and physical performance</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>CBC and differential count</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Marrow aspirate and biopsy</td>
<td>When clinically indicated or with unclear cytopenia</td>
<td>Desirable</td>
</tr>
<tr>
<td>Serum chemistry, serum immunoglobulin, and direct antiglobulin test</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Infectious disease status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Additional tests before treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH for del(13q), del(11q), del(17p), 12p rearrangements in peripheral blood lymphocytes</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)</td>
<td>Not generally indicated</td>
<td>Desirable</td>
</tr>
<tr>
<td><strong>TP53</strong> mutation</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td><strong>IGHV</strong> mutational status</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Serum β2-microglobulin</td>
<td>Desirable</td>
<td>Always</td>
</tr>
<tr>
<td>CT scan of chest, abdomen, and pelvis</td>
<td>Not generally indicated</td>
<td>Desirable</td>
</tr>
<tr>
<td>MRI/PET scans</td>
<td>Not generally indicated</td>
<td>Not generally indicated</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Possible</td>
<td>Not generally indicated</td>
</tr>
</tbody>
</table>

**Phase 3 clinical trial enrollment**

Patients should be stratified for **IGHV**-mutated disease vs wild-type disease. If it is not possible to stratify prospectively, then stratified subgroup analysis should be as a planned. If the specific patient subgroup is not excluded, they should be stratified or analyzed as a subgroup analysis based upon whether they have leukemia cells with 17p or 11q deletions, and **TP53** mutations.

---

3. International Workshop on Chronic Lymphocytic Leukemia. 2021出来的指南

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**Abdominal ultrasound**

Possible | Not generally indicated

CBC, complete blood count; **CLL**, chronic lymphocytic leukemia; del, deletion; **FISH**, fluorescence in situ hybridization; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; PET, positron emission tomography.
However, 5-year follow-up data from the phase 3 MURANO trial (NCT02005471) demonstrated that patients with relapsed/refractory CLL who were treated with venetoclax plus rituximab and had mutated *IGHV* had twice as fast a doubling rate in CLL growth compared with patients with unmutated *IGHV* (P = .0057).3

"In the context of venetoclax therapy, *IGHV* mutations may in fact become a useful marker," Ahn said. "More data are needed to determine if *IGHV* mutation status has prognostic value in light of fixed-duration therapy and whether this would eventually translate into a difference in outcome, especially survival," she added.

Coutre echoed this sentiment, stating that, "*IGHV* mutation status may be predictive of response duration with time-limited therapy. We are starting to see a separation between [patients with] mutated and unmutated [*IGHV* receiving fixed-duration treatment] in distinction to continuous BTK [treatment]; mutational status doesn’t seem to make a difference and both groups of patients continue to benefit equally as they stay on therapy."

**TP53 ABERRATIONS**

TP53 aberrations are defined as 17p deletions by hierarchical FISH or TP53 mutations by sequencing plus FISH. The presence of TP53 aberrations confers a more aggressive disease state and an unfavorable response to chemoimmunotherapy.

"TP53 aberrations have been the strongest negative predictor of survival in CLL. These patients do very poorly with chemoimmunotherapy," Ahn said. Inferior PFS has been observed with ibrutinib (Imbruvica) treatment in patients with TP53-mutated CLL compared with patients with wild-type CLL. Findings from the phase 3 RESONATE CLL vs TP53 trial (NCT01578707) showed that at a median follow-up of 6 years, the median PFS with ibrutinib was 41 months in patients with TP53 mutations by sequencing plus FISH. The presence of TP53 aberrations confers a more aggressive disease state and an unfavorable response to chemoimmunotherapy.

"TP53 aberrations have been the strongest negative predictor of survival in CLL. These patients do very poorly with chemoimmunotherapy," Ahn said. Inferior PFS has been observed with ibrutinib (Imbruvica) treatment in patients with TP53-mutated CLL compared with patients with wild-type CLL. Findings from the phase 3 RESONATE CLL vs TP53 trial (NCT01578707) showed that at a median follow-up of 6 years, the median PFS with ibrutinib was 41 months in patients with TP53-mutated CLL compared with 57 months in patients with TP53 wild-type CLL (HR, 1.7; 95% CI, 1.2-2.6).7

"With continuous BTK inhibitor therapy, we seem to get the greatest benefit in [patients with TP53 wild-type CLL]. With the time-limited therapy, we don’t seem to get as long of a benefit, but it may play an important role when choosing initial therapy for this group of patients," Coutre said.

**FUTURE DIRECTIONS IN CLL**

Currently, the standard of care for patients with asymptomatic disease is active surveillance, irrespective of risk.2 The phase 3 EVOLVE CLL/SLL trial (NCT04269902) is recruiting patients with newly diagnosed, high-risk, asymptomatic CLL or small lymphocytic lymphoma (SLL) to evaluate the utility of early vs delayed treatment with venetoclax/obinutuzumab.4 Overall survival will serve as the primary end point of the study.

"Does early intervention change the natural history of the disease? It’s a very important question for many of our patients," Coutre said.

"As the treatment landscape of CLL is rapidly evolving, the research around developing a better prognostic marker should evolve as well. ■

For full list of references, see the article at OncologyLive.

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New Strategies Are Needed for Patients With NRAS-Mutant Melanoma

by ANITA T. SHAFFER

ALTHOUGH THERE HAS BEEN dramatic progress in the treatment landscape for metastatic melanoma over the past decade, many patients whose tumors harbor NRAS mutations have not shared in the improved outcomes. There are no therapies designed to directly target this alteration, and some studies show a limited benefit from immunotherapy.1,2

Activating NRAS mutations, which are detected in approximately 20% of cutaneous melanoma cases, are among the most frequently observed driver mutations in patients with the malignancy.1,3 Investigators are exploring several novel strategies to address the needs of this population, including the development of agents that target different nodes of the MAPK cell-signaling network that includes NRAS alterations and is activated in nearly all cases of cutaneous melanoma.3,4

Genentech is testing belvarafenib, a pan-RAF kinase inhibitor, in patients with NRAS-mutant advanced melanoma.5 Novartis is evaluating LXH254, a RAF inhibitor that is highly selective for BRAF and CRAF, in patients with NRAS-mutant melanoma.6 Early-phase studies employing combinations that pair approved MEK inhibitors with other targeted agents also are underway (TABLE3,5,6).

PREVALENCE OF NRAS MUTATIONS

In the 1980s, NRAS became the first oncogene described in melanoma after investigators analyzed DNA from melanoma cell lines.7,8 NRAS is a member of the RAS superfamily of guanosine triphosphate–binding proteins, which includes KRAS and HRAS. In melanoma, activated NRAS proteins leverage receptor tyrosine kinases to stimulate intracellular signaling in the MAPK pathway, which promotes cell proliferation and growth (FIGURE).5,7

NRAS mutations are the most frequently observed of the RAS isoforms in cutaneous melanomas. Whereas KRAS and HRAS mutations are detected in 2% and 1% of cutaneous melanomas, respectively, NRAS mutations are found in 20%, most commonly in the exon 1 (G12 and G13 substitutions) and exon 2 link (Q61 substitution).1,1

NRAS mutations, however, have been overshadowed by BRAF alterations. Nearly 40% of patients with melanoma have tumors harboring a BRAF mutation, with BRAF V600 aberrations as the most prevalent subtype, according to a whole-genome sequencing analysis by the Australian Melanoma Genome Project. That makes BRAF the most frequently mutated gene, followed by NRAS.1,9

Investigators have learned that patients with NRAS-mutated melanomas are generally older when they receive a diagnosis (>55 years) with thicker tumors that are more likely to be located on the extremities and greater rates of mitosis than patients with BRAF-mutated or BRAF wild-type tumors. Although activating mutations of BRAF and NRAS typically exist

### TABLE. Ongoing Clinical Studies Targeting NRAS-Mutant Melanoma3,5,6

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Study population</th>
<th>Phase; ClinicalTrials.gov identifier</th>
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<tr>
<td><strong>MEK inhibitor–based strategies</strong></td>
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<tr>
<td>Trametinib plus hydroxychloroquine (autophagy inhibition)</td>
<td>Metastatic or locally advanced unresectable NRAS-mutant melanoma progressing during or after a first-line ICI therapy</td>
<td>Phase 1b/2; NCT03979651</td>
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<td>Binimetinib monotherapy</td>
<td>Locally advanced and unresectable or metastatic cutaneous melanoma, with BRAF V600E or NRAS mutations</td>
<td>Phase 2; NCT01320085*</td>
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<td>HL-085 monotherapy</td>
<td>Unresectable stage III/IV melanoma with NRAS mutation</td>
<td>Phase 1/2; NCT03973151</td>
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<td>FCN-159 monotherapy</td>
<td>Unresectable advanced stage III/IV melanoma with NRAS aberration or mutation</td>
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<td><strong>RAF inhibitor–based combinations</strong></td>
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<td>LXH254 in combination with LIT462 (ERK1/2 inhibitor), trametinib, or ribociclib (CDK4/6 inhibitor)</td>
<td>Previously treated unresectable or metastatic with BRAF V600 or NRAS mutations</td>
<td>Phase 2; NCT04417621</td>
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<tr>
<td>LXH254 in combination with LIT462, trametinib, or ribociclib</td>
<td>Advanced or metastatic NRAS-mutant melanoma or NSCLC with KRAS or BRAF mutation</td>
<td>Phase 1b; NCT02974725</td>
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<tr>
<td>Belvarafenib as monotherapy and in combination with cobimetinib (MEK inhibitor) or cobimetinib plus atezolizumab (anti–PD-L1 inhibitor)</td>
<td>NRAS-mutant advanced melanoma after anti–PD-1/ PD-L1 therapy</td>
<td>Phase 1; NCT04835805</td>
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<td>Belvarafenib in combination with cobimetinib</td>
<td>Locally advanced or metastatic melanoma with NRAS, KRAS, or RAF mutations; KRAS-mutant NSCLC, pancreatic cancer, or CRC; BRAF V600–mutant CRC; other solid tumors with RAS, RAF, BRAF mutations*</td>
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<td><strong>FAK inhibitor–based therapy</strong></td>
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<td>Metastatic uveal or NRAS-mutant melanoma</td>
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CRC, colorectal cancer; ICI, immune checkpoint inhibitor; NSCLC, non–small cell lung cancer.

*Study is active but no longer recruiting participants.

*Belvarafenib also has been identified as HM95573, GDC-5573, and RG6185.

The combination of belvarafenib and cetuximab, an EGFR inhibitor, is being tested in dose-escalation and expansion cohorts in patients with CRC harboring BRAF V600 mutations.
independent of each other, both mutations are associated with aggressive melanoma and shorter survival compared with tumors that are wild-type for both aberrations.7

Despite a growing knowledge base about NRAS mutations, these alterations have proved more difficult to target than BRAF mutations. The population of patients with NRAS mutations is among those with melanoma in need of new therapeutic approaches, even amid the remarkable gains that have been made against the malignancy, experts say.

**A DECADE OF PROGRESS**

Since 2010, the melanoma field has witnessed a “golden decade,” according to Caroline Robert, MD, PhD, head of the dermatology unit at Gustave Roussy and codirector of the melanoma research unit at Paris-Sud University in Villejuif, France. Robert, a 2018 Giants of Cancer Care award winner in the melanoma category, reviewed progress in the treatment paradigm during an industry-sponsored symposium at the European Society for Medical Oncology (ESMO) 2021 Congress.2

At the start of 2010, no systemic therapy had been shown to significantly extend survival in patients with metastatic melanoma, Robert said. The standard of care was chemotherapy with dacarbazine, which demonstrated a median overall survival (OS) of 231 days or 7.6 months, she noted. Today, the paradigm includes options for the adjuvant setting as well as immune checkpoint inhibitor (ICI) and targeted therapy for metastatic disease.2

The progress that has been made is evident in recent long-term analyses of pivotal clinical trial data. The median OS ranged from 22.5 months to 33.6 months for patients with advanced melanoma with BRAF V600 mutations treated with combination regimens of BRAF and MEK inhibitors, according to 5-year trial data. For patients with advanced melanoma who receive ICI therapy, the median OS reached 38.7 months with single-agent pembrolizumab (Keytruda), a PD-1 inhibitor, in a 5-year follow-up analysis of pooled data from the phase 3 KEYNOTE-006 trial (NCT01866319).2

Meanwhile, patients with previously untreated advanced melanoma who received a combination of nivolumab (Opdivo), a PD-1 inhibitor, plus ipilimumab (Yervoy), a CTLA-4 inhibitor, achieved a median OS of 72.1 months in the phase 3 CheckMate 067 trial (NCT01844505), with 50% of the patients surviving 5 years, according to 6.5-year follow-up data.2 That outcome is nearly 10 times longer than the median OS was with dacarbazine, Robert noted. “This is huge, a huge improvement,” she said.

Nevertheless, Robert said, “it also means there are 50% of patients who have died of their melanoma in these 5 years and now it is for these patients that we have to work and understand how to optimize our treatments.”

Robert said there are several groups of patients not achieving long-term survival in the evolving melanoma landscape. These include patients who develop primary or acquired resistance to therapy, are unable to tolerate or receive current therapies, have high lactate dehydrogenase levels or a high disease burden, have brain and/or liver metastases, and have other melanoma subtypes such as mucosal melanoma.

**NEED FOR MORE OPTIONS**

Although targeted therapy and ICI therapy are twin pillars of the melanoma treatment paradigm, the National Comprehensive Cancer Network (NCCN) guidelines panel considers recommended ICI options as appropriate first-line systemic therapy for patients with distant metastatic or unresectable melanoma regardless of BRAF mutation status. Preferred ICI regimens are single-agent nivolumab or pembrolizumab or the combination of ipilimumab plus nivolumab.10

For patients with activating BRAF V600 mutations, 3 regimens combining BRAF and MEK inhibitors also are category 1 choices: dabrafenib (Tafinlar) plus trametinib (Mekinist), vemurafenib (Zelboraf) plus cobimetinib (Cotellic), and encorafenib (Braftovi) plus binimetinib (Mektovi).

However, there is evidence that ICI therapy is not similarly effective across molecular subtypes. Patients with BRAF V600 wild-type tumors represent a significant population with unmet needs, including those who receive ICI therapy.
in the front line, Matteo C. Carlino, MBBS, FRACP, PhD, said during a presentation at the 2021 American Society of Clinical Oncology Annual Meeting.1 Carlino is a medical oncologist at Westmead Hospital, Blacktown Hospital, and the Melanoma Institute Australia and a clinical associate professor at Sydney Medical School, University of Sydney.

In the broad category of patients without BRAF mutations, ICI therapy outcomes are less beneficial than for those with BRAF V600-mutated malignancy, Carlino said. In CheckMate 067, outcomes were worse for patients without BRAF mutations. At 5 years, the OS rates for patients with BRAF-mutated compared with BRAF wild-type tumors were 60% vs 48%, respectively, for those who received the combination of nivolumab plus ipilimumab, 46% vs 43% for participants in the single-agent nivolumab arm, and 30% vs 25% in the ipilimumab-monotherapy group. Progression-free survival (PFS) rates and median OS also were higher for patients with BRAF mutations compared with BRAF wild-type tumors.11

“In the BRAF wild-type subgroup, approximately two-thirds of patients have progressed by 5 years and over 50% of patients have died in that time frame,” Carlino said. “As such there’s a significant patient population of BRAF wild-type patients who require further treatment beyond an anti-PD-1 agent alone or in combination with ipilimumab.”

Specifically for NRAS mutations, clinical trial findings are more difficult to interpret. “There are conflicting data regarding the prognostic impact of NRAS mutations, with some studies showing no impact, other studies saying [patients with] NRAS mutations have a poorer survival, and there are some data to suggest there is a higher likelihood of response to immune checkpoint inhibition with NRAS mutations,” Carlino said.

Findings from the pivotal trials that led to FDA approval of ICI therapies did not specify outcomes for patients with NRAS mutations, and much of what is known about the impact for this population comes from retrospective analyses, according to melanoma specialists from Vall d’Hebron Institute of Oncology in Barcelona, Spain. In findings from 3 ICI studies, patients with NRAS mutations had a lower rate of median OS in 1 study than participants with NRAS wild-type tumors (21 vs 33 months; P = .034), a higher rate in another (19.5 vs 15.2 months; P = .51), and no significant difference in the third study (32 vs 27 months; P not specified).1

MEK INHIBITORS TESTED

Investigators searching for new strategies for patients in underserved subgroups are focusing on the MAPK pathway, as 98% of cases in the Australian genomic study had at least 1 mutation in the network, Carlino noted. For NRAS-mutated tumors, some progress has been made with inhibiting MEK, another node in the pathway. However, MEK inhibition has shown limited efficacy as monotherapy, and combinations pairing these agents with CDK4/6 inhibitors, pan-RAF inhibitors, or PI3K inhibitors are being studied.1,3

**Binimetinib**

One MEK inhibitor that has shown positive results as a single agent is binimetinib, which demonstrated an improvement in PFS compared with dacarbazine for patients with NRAS-mutated melanoma. Binimetinib has been incorporated into the NCCN guidelines as a category 2B option for patients with this alteration who have progressed after prior ICI therapy.10

In the phase 3 NEMO trial (NCT01763164), 402 patients with unresectable stage IIIC or stage IV NRAS-mutated melanoma who were either previously untreated or had progressed after prior immunotherapy were randomized 2:1 to receive either binimetinib at 45 mg orally twice daily or dacarbazine at 1000 mg/m² intravenously every 3 weeks.12

After a median follow-up of 1.7 months, the median PFS was 2.8 months (95% CI, 2.8-3.6) for those treated with binimetinib (n = 269) compared with 1.5 months (95% CI, 1.5-1.7) for participants given dacarbazine (n = 133), which translated into a statistically significant advantage for the targeted agent (HR, 0.62; 95% CI, 0.47-0.80; 1-sided P < .001). The overall response rate (ORR) was 15% (95% CI, 11%-20%) with binimetinib compared with 7% (95% CI, 3%-13%) with dacarbazine.

The benefit with binimetinib was more pronounced for participants who received previous immunotherapy. In this group, the median PFS with binimetinib was 5.5 months (95% CI, 2.8-7.6) compared with 1.6 months (95% CI, 1.5-2.8) for those who had dacarbazine. Moreover, the confirmed...
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EXKIVITY™

mobocertinib
40 mg capsules

The first oral therapy for EGFR Exon20 insertion+ mNSCLC patients post platinum-based chemotherapy

INDICATION

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLONGATION and TORSADES DE POINTES

See full prescribing information for complete boxed warning.

- EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation.

- Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc.

- Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation.

WARNINGS AND PRECAUTIONS

QTc Prolongation and Torsades de Pointes

EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250-patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs), 1.2% of patients had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with baseline QTc greater than 470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation.

Interstitial Lung Disease (ILD)/Pneumonitis

EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population, ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.

Cardiac Toxicity

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure, which can be fatal. In the pooled EXKIVITY safety population, heart failure occurred in 2.7% of patients including 1.2% Grade 3 events, 0.4% Grade 4 events, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%),
IMPORTANT SAFETY INFORMATION (CONT’D)

first-degree atrioventricular block (0.4%), second-degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%), and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY. Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity.

Diarrhea
EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population, diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days, but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an anti-diarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, EXKIVITY 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 nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY.

ADVERSE REACTIONS
The most common (>20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

DRUG INTERACTIONS

CYP3A Inducers
Co-administration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations, which may reduce EXKIVITY antitumor activity. Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

CYP3A Substrates
Co-administration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of hormonal contraceptives with EXKIVITY. Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information.

Prolonged QTc Interval
EXKIVITY can cause QTc interval prolongation. Co-administration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs.

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Advise pregnant women of the potential risk to a fetus.

Females and Males of Reproductive Potential
Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

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

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-844-217-6668 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of Prescribing Information, including Boxed Warning, on the following pages.

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer.
**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**EXKIVITY™ (MOBOCERTINIB)**

1 **INDICATIONS AND USAGE**

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1)], whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 **DOSE AND ADMINISTRATION**

2.1 Patient Selection:

Select patients with locally advanced or metastatic NSCLC for treatment with EXKIVITY based on the presence of EGFR exon 20 insertion mutations [see Clinical Studies (14)]. Information on FDA-approved tests is available at: [http://www.fda.gov/Compliance][2].

2.2 Recommended Dosage:

The recommended dosage of EXKIVITY is 160 mg orally once daily until disease progression or unacceptable toxicity.

Take EXKIVITY with or without food [see Clinical Pharmacology (12.3)], at the same time each day. Swallow EXKIVITY capsules whole. Do not open, chew or dissolve the contents of the capsules.

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time. If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

2.3 Dosage Modifications for Adverse Reactions:

EXKIVITY dose reduction levels for adverse reactions are summarized in Table 1.

### Table 1: Recommended EXKIVITY Dose Reductions

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<thead>
<tr>
<th>Dose Reductions</th>
<th>Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>120 mg once daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>80 mg once daily</td>
</tr>
</tbody>
</table>

Recommended dosage modifications of EXKIVITY for adverse reactions are provided in Table 2.

### Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc Interval Prolongation and Torsades de Pointes</td>
<td>Grade 2</td>
<td>First Occurrence&lt;br&gt;Withhold EXKIVITY until ≤ Grade 1 or baseline.&lt;br&gt;Upon recovery, resume EXKIVITY at the same dose.&lt;br&gt;Reurrence&lt;br&gt;Withhold EXKIVITY until ≤ Grade 1 or baseline.&lt;br&gt;Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>(QTc interval 481-500 msec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>First Occurrence&lt;br&gt;Withhold EXKIVITY until ≤ Grade 1 or baseline.&lt;br&gt;Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>(QTc interval &gt;501 msec or QTc interval increase of &gt;60 msec from baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td>Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>(Torsades de Pointes, polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial Lung Disease (ILD)/pneumonitis</td>
<td>Any grade</td>
<td>Withhold EXKIVITY if ILD/pneumonitis is suspected.&lt;br&gt;Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Adverse Reactions</th>
<th>Intolerable or recurrent</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Grade 2</td>
<td>Withhold EXKIVITY until ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td>[see Warnings and Precautions (5.4)]</td>
<td>Grade 3</td>
<td>Permanently discontinue EXKIVITY.</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal

* Graded per Common Terminology Criteria for Adverse Events Version 5.0

2.4 Dosage Modifications for Moderate CYP3A Inhibitors:

Avoid concomitant use of moderate CYP3A inhibitors with EXKIVITY. If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce the EXKIVITY dose by approximately 50% (i.e., from 160 to 80 mg, 120 to 40 mg, or 80 to 40 mg) and monitor the QTc interval more frequently. After the moderate CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume EXKIVITY at the dose taken prior to initiating the moderate CYP3A inhibitor [see Drug Interactions (7.1)].

2.5 Dosage Modifications for Moderate CYP3A Inducers:

Avoid coadministration of moderate CYP3A inducers during treatment with EXKIVITY. If coadministration of a moderate CYP3A inducer cannot be avoided, gradually increase the EXKIVITY once-daily dose in 40-mg increments after 7 days of treatment with EXKIVITY and the moderate CYP3A inducer as tolerated, up to a maximum of twice the EXKIVITY dose that was tolerated prior to initiating the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, resume the EXKIVITY dose that was tolerated prior to initiating the moderate CYP3A inducer.

5 **WARNINGS AND PRECAUTIONS**

5.1 QTc Prolongation and Torsades de Pointes:

EXKIVITY can cause life-threatening heart rate–corrected QTc (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation [see Warnings and Precautions (5.1)].

Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc [see Warnings and Precautions (5.1), Drug Interactions (7.1, 7.3)].

Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation [see Dosage and Administration (2.3)].

### Table 2: Recommended EXKIVITY Dosage Modifications for QTc Prolongation and Torsades de Pointes

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Ejection Fraction or Heart Failure</td>
<td>Grade 2</td>
<td>Withhold EXKIVITY until ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td>[see Warnings and Precautions (5.3)]</td>
<td>Grade 3</td>
<td>Permanently discontinue EXKIVITY.</td>
</tr>
</tbody>
</table>

5.2 Intestinal Lung Disease (ILD)/Pneumonitis:

EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)], ILD/pneumonitis occurred in 4.3% of patients including 0.9% Grade 3 events and 1.2% fatal events.

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed [see Dosage and Administration (2.3)].

5.3 Cardiac Toxicity:

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)], heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes [see Warnings and Precautions (5.1)].
5.4 Diarrhea: EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)], diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity [see Dosage and Administration (2.3)].

5.5 Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryolethality at maternal exposures 1.7 times the human exposure based on area under the curve (AUC) at the 160-mg once-daily clinical dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use contraception during treatment with EXKIVITY [see Drug Interactions (7.2)] and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY [see Use in Specific Populations (8.1, 8.3)] and for 1 week after the last dose of EXKIVITY [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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 pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to EXKIVITY as a single agent at a dose of 160 mg orally once daily in 256 patients, including 114 patients with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC from Study AP32788-15-101, and patients with other solid tumors. Forty-eight percent (48%) were exposed for 6 months or longer and 12% were exposed for greater than one year. The most common (>20%) adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (>2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

EGFR Exon 20 Insertion Mutation–Positive Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 with EGFR exon 20 insertion mutation–positive locally advanced or metastatic NSCLC who received prior platinum-based chemotherapy [see Clinical Studies (14)]. Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment; significant, uncontrolled, active cardiovascular disease; or prolonged QTc interval were excluded from enrollment in this trial. A total of 114 patients received EXKIVITY 180 mg once daily until disease progression or unacceptable toxicity; 88% were exposed for 6 months or longer and 14% were exposed for greater than 1 year. Serious adverse reactions occurred in 46% of patients who received EXKIVITY. Serious adverse reactions in ≥2% of patients included diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. Fatal adverse reactions occurred in 1.8% of patients who received EXKIVITY, including cardiac failure (0.9%), and pneumonitis (0.9%).

Permanent discontinuation occurred in 17% of patients who received EXKIVITY. Adverse reactions requiring permanent discontinuation of EXKIVITY in at least ≥2% of patients included diarrhea and nausea. Dosage interruptions of EXKIVITY due to an adverse reaction occurred in 51% of patients. Adverse reactions which required dosage interruption in ≤5% of patients included diarrhea, nausea, and vomiting. Digestive disorders are reactions to food (e.g., nausea, vomiting, diarrhea, abdominal pain, constipation, flatulence, anorexia) and reactions to medications (e.g., mouth dryness, mouth ulceration). Digestive disorders are often associated with other systemic reactions (e.g., rash, conjunctivitis, cough, dyspnea).

Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXKIVITY</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>N = 114</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>92</td>
<td>22</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
<td>4.4**</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>2.6**</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39</td>
<td>0.9**</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY**</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>N = 114</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased red blood cells</td>
<td>59</td>
<td>3.5</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101 (cont’d)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY** (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades* (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>5.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Grades per NCICTC v5.0  ** The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from baseline.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on EXKIVITY

** Strong or Moderate CYP3A Inhibitors**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations [see Clinical Pharmacology (12.3)], which may increase the risk of adverse reactions, including QTc interval prolongation.</td>
<td>Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs [see Dosing and Administration (2.4), Warnings and Precautions (5.1)].</td>
</tr>
</tbody>
</table>

** Strong or Moderate CYP3A Inducers**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations [see Clinical Pharmacology (12.3)], which may reduce EXKIVITY anti-tumor activity.</td>
<td>Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.</td>
</tr>
</tbody>
</table>

7.2 Effect of EXKIVITY on Other Drugs

** CYP3A Substrates**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates [see Clinical Pharmacology (12.3)], which may reduce the efficacy of these substrates.</td>
<td>Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of another CYP3A inhibitor with EXKIVITY is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product prescribing information.</td>
</tr>
</tbody>
</table>

7.3 Drugs that Prolong the QTc Interval

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXKIVITY can cause QTc interval prolongation [see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)]. Coadministration of EXKIVITY with drugs known to prolong the QT interval may increase the risk of QTc interval prolongation [see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)].</td>
<td>Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs [see Warnings and Precautions (5.1)].</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

** Risk Summary **

Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology (12.1)], EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryo lethality (embryo-fetal death) and maternal toxicity at plasma exposures approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose [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% to 4% and 15% to 20%, respectively.

<table>
<thead>
<tr>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Data</td>
</tr>
</tbody>
</table>

In an embryo-fetal development study, once-daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose). Adverse effects on embryo-fetal development at this dose level included embryolethality due to post-implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high-dose level (10 mg/kg).

8.2 Lactation

** Risk Summary **

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

8.3 Females and Males of Reproductive Potential

EXKIVITY can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

** Pregnancy Testing **

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

** Contraception **

- Females: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective [see Drug Interactions (7.2)].

- Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

** Infertility **

Based on animal studies, EXKIVITY may impair fertility in males and females of reproductive potential [see Preclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 114 patients [see Clinical Studies (14)] who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (89% vs 47%) and serious adverse reactions (84% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

8.6 Renal Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² by Modification of Diet in Renal Disease [MDRD] equation). The recommended dosage of EXKIVITY has not been established for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN]) and aspartate aminotransferase [AST] > ULN or total bilirubin >1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin ≥1.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY has not been established for patients with severe hepatic impairment (total bilirubin ≥3 times ULN and any AST) [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information). QTc Interval Prolongation and Torsades de Pointes

Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see Warnings and Precautions (5.1)].

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain [see Warnings and Precautions (5.2)].

Cardiac Toxicity

Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see Warnings and Precautions (5.3)].

Diabetes

Inform patients that EXKIVITY may cause diabetes, which may be severe in some cases and should be treated promptly. Advise patients to have antidiabetic medicine readily available and promptly start antidiabetic treatment (e.g., lopinamide), increase oral fluids and electrolyte intake, and contact their healthcare provider if diabetes occurs [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].

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

Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose [see Use in Specific Populations (8.3)].

Lactation

Advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose [see Use in Specific Populations (8.2)].

Infertility

Advise females and males of reproductive potential that EXKIVITY may impair fertility [see Use in Specific Populations (8.3)].

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)]. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

Missed Dose

Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day [see Dosage and Administration (2.2)].
advanced solid tumors. The median PFS among these patients was 24.9 weeks (95% CI, 4.8-84.0) with a median duration of response of 17.8 weeks (95% CI, 3.3-37.3). In a dose-expansion study (NCT03118817), 2 of 10 patients (20.0%) with NRAS-mutant melanoma reached a best overall response.\(^5\)

In ongoing research, the combination of belvarafenib plus cobimetinib, a MEK inhibitor, is being tested in patients with NRAS-mutated melanoma as part of an expansion cohort of a phase 1 study (NCT03284502) in locally advanced or metastatic solid tumors that have not responded to prior therapies or do not have standard treatment options. Other cohorts of this study focus on patients with KRAS, RAS, RAF, or BRAF V600 mutations.

In another phase 1 study (NCT04835805), belvarafenib is being evaluated as monotherapy and in combination with either cobimetinib or cobimetinib plus atezolozumab (Tecentriq), a PD-L1 inhibitor, in patients with NRAS-mutant advanced melanoma who have received prior anti-PD-1/PD-L1 ICI therapy.

**LHX254**

Results of preclinical studies in mouse models show that LHX254 strongly inhibits 2 members of the RAF family, BRAF and CRAF, but has limited activity against its 2 members of the RAF family, BRAF and CRAF. Investigators theorize that LHX254’s sparing of CRAF may improve tolerability in normal tissues and make the agent a good candidate for combination therapy targeting downstream effectors, including MEK, ERK, or CDK4/6.\(^6\)

In a first-in-human phase 1 study (NCT02607813), LHX254 monotherapy was tested across 9 dosing levels in 81 patients with advanced solid tumors harboring at least 1 MAPK pathway alteration. Overall, 2 patients with KRAS- and BRAF-mutant disease achieved confirmed partial responses and 34.6% of participants reached stable disease. The study included 8 participants with skin melanoma but results for this cohort were not separately reported.\(^16\)

LHX254 is being evaluated in combination with LTT462, an ERK1/2 inhibitor; trametinib; or ribociclib in patients with previously treated unresectable or metastatic melanoma harboring BRAF V600 or NRAS mutations in a phase 2 study (NCT04417621). Investigators aim to recruit 320 participants.\(^1\)
A New Era of Precision Medicine Takes Shape in Prostate Cancer

by CHRISTINA T. LOGUIDICE

PROSTATE CANCER IS A **highly heterogeneous** disease, with individual tumor cells having distinct genomic and phenotypic characteristics, resulting in a great deal of variability in patients' disease course. Although some prostate cancers are slow growing and amenable to being safely monitored, others are more rapidly growing and aggressive, potentially proving fatal without prompt and effective interventions. Subsequently, being able to precisely determine the nature of the disease is crucial to prevent overtreatment of more benign disease and undertreatment or suboptimal treatment of more aggressive disease, which can be fatal.

During a recent OncLive Peer Exchange®, a panel of prostate cancer experts discussed how precision medicine is helping ensure more patients with prostate cancer are appropriately treated. They discussed newer diagnostic modalities, such as liquid tumor profiling, and examined the role of prostate-specific membrane antigen (PSMA) for diagnostic imaging and treatment via targeted radionuclides, which are ushering in a potentially new approach to prostate cancer management known as theranostics. “There’s such significant heterogeneity [in prostate cancer] that our ability to pick therapy for a given individual should be based on some selection, and that’s what precision medicine means to me,” Sandy Srinivas, MD, said.

**USING GENOMIC MARKERS TO PUT PRECISION MEDICINE INTO PRACTICE**

Precision medicine is not a novel concept in the treatment of prostate cancer. "Precision medicine goes back to the time of ADT [androgen deprivation therapy] because targeting the androgen receptor (AR) was one of the very first precise ways of targeting cancer," Alicia K. Morgans, MD, MPH, said. Although ADT remains the backbone of treatment for this patient population, a variety of other actionable targets have emerged in recent years, including *BRCA2* mutations and tumor mutational burden or microsatellite instability (MSI), which can be targeted with PARP inhibitors and pembrolizumab (Keytruda), respectively.

The challenge with these actionable targets, however, is that relatively few patients with prostate cancer have them. In studies assessing the frequency of *BRCA* mutations, the prevalence of germline or somatic *BRCA2* mutations in prostate cancer has ranged from 5.3% to 13%.1 MSI-high tumors are even less common, with investigators reporting an incidence of this actionable target in only 3.1% of patients.2

“I haven’t yet [encountered] a patient [with prostate cancer] who has MSI-high [disease],” Srinivas said, adding that she looks for this marker in patients with advanced disease who require treatment after AR therapy and are not good candidates for chemotherapy. “It’s at that point that I’ve definitely looked at prior tissue and liquid biopsies…. That’s a time to look for these markers because the patients who have this will have such an amazing therapeutic option, one where they could have a response that could be more long lasting.”

The panelists noted several challenges when it comes to characterizing prostate cancer...
cancer via tissue or blood sampling, as many patients have bone metastases but no accessible lymph nodes or visceral metastases that can be readily biopsied and sequenced. Subsequently, it can be particularly challenging identifying actionable somatic mutations. “Optimally, for any given patient, it’s best to use a plethora of different tools,” Scott T. Tagawa, MD, MS, said, explaining that each option has advantages that can help provide a more complete picture of the tumor profile for a particular patient. Tagawa noted that bone biopsies are often overlooked as an option but can be a valuable source for high-quality DNA and RNA for tumor sequencing that may be used to detect actionable alterations and resistance mechanisms in patients with bone metastases. In a bone biopsy study he was involved with, the material obtained via bone biopsy successfully confirmed prostate cancer in 85.7% of cases (n = 60/70 bone biopsies), with whole-exome sequencing possible in 81.7% of cases and RNA sequencing possible in 33.3% of cases. Recurrent alterations known to occur in prostate cancer were observed, including AR mutation (4.0%), PTEN deletion (10.2%), TP53 mutation (14.3%), BRCA2 mutation (10.2%), and SPOP mutation (4.0%).

Although tissue biopsy is still considered the gold standard for identifying actionable genetic markers and providing the most in-depth information, Tagawa explained that the heterogeneity of prostate cancer poses challenges. “We get a great depth of whatever is in the needle, and that’s it. The same tumor in a different location may be a little different,” he said, adding that as a result, blood-based biomarkers can be a useful adjunct for obtaining information about tumors, provided the patient does not have a hematologic malignancy attributed to a germline mutation. With blood-based biomarkers, however, there are differences between circulating tumor DNA and cell-free DNA, he noted. “Circulating tumor DNA, where we have a germline-matched sample, is very good. It’s not as sensitive, but we can really trust those results. When we have cell-free DNA without a germline sample, we have to worry about clonal hematopoiesis.”

Morgans agreed and emphasized the importance of germline testing. “All patients with advanced prostate cancer, high-risk localized or metastatic hormone-sensitive and beyond, are eligible for germline testing at this point in time. They’re not just eligible—it’s recommended,” she said.

**MOVING TOWARD PHENOTYPIC MARKERS IN PROSTATE CANCER: PSMA**

Phenotypic biomarkers are an emerging area in cancer medicine. Unlike genetic markers that include mutations and other cellular aberrations, phenotypic biomarkers are findings that can be detected on the cell, usually via an imaging study. These findings can help predict prognosis and responsiveness to therapy. One phenotypic biomarker that is already changing the prostate cancer landscape is PSMA, with 2 PSMA-targeted diagnostic agents recently receiving FDA approval and opening the door for patients to be treated with PSMA-targeted molecules. “A lot of times, the focus has been on detecting disease, but now the idea of using imaging to select patients for treatment is real,” Phillip J. Koo, MD, said.

PSMA is a transmembrane protein with 100- to 1000-fold higher expression by prostate cancer cells than normal prostate cells. Although PSMA expression has been observed in almost all types of prostate cancer, expression is highest in adenocarcinomas. Expression also increases progressively in higher-grade disease, metastatic disease, and castration-resistant prostate cancer (CRPC), suggesting PSMA may play a role in the identification of prostate cancer progression. Close to 85% of patients with advanced disease have positive PSMA expression,” Srinivas said. “As [patients] get more treatment, perhaps with AR-directed therapy, there’s increased expression of PSMA.” For example, study results showed a median 45% increase in intensity of PSMA standard uptake value was by day 9 of treatment with ADT.

The 2 FDA-approved PSMA-targeted diagnostic agents are gallium 68 (~68GA)PSMA-11, which was approved in December 2020, and DCFPyL F 18 (Pylarify), a fluorine 18-based PyL approved in May. The approval of ~18F-DCFPyL is particularly notable because it is enabling PSMA imaging to become available nationwide. In contrast, access to ~68GA PSMA-11 has been limited to the University of California in San Francisco and Los Angeles. “We’re seeing nationwide commercialization of the PyL compound because of the isotope, which allows it to be distributed across the United States pretty easily. This is going to really change what we see in terms of access,” Koo said.

Approval of ~18F-DCFPyL as a positron emission tomography (PET)/CT agent was based on data from 2 studies: OSPREY (NCT02981368) and CONDOR (NCT03739684).

**OSPREY trial**

In the phase 2/3 OSPREY trial, 2 patient populations underwent ~18F-DCFPyL PET/CT scanning: cohort A, which included men with high-risk prostate cancer undergoing radical prostatectomy with pelvic lymphadenectomy (n = 252), and cohort B, which included men with suspected recurrent/metastatic prostate cancer on conventional imaging (n = 93). All scans were evaluated by 3 blinded central readers, with the scans’ diagnostic performance determined by comparing the imaging results with the histopathology findings. In cohort A, ~18F-DCFPyL PET/CT had a median specificity of 97.9% and median sensitivity of 40.3%, the latter of which did not meet the prespecified end point. The median positive predictive value was 86.7% and the median negative predictive value was 83.2%. In cohort B (median prostate-specific antigen [PSA], 11.3 ng/mL), the median sensitivity and positive predictive value for extraprostatic lesions were 95.8% and 81.9%, respectively.

**CONDOR trial**

In the phase 3 CONDOR trial, 208 men with rising PSA at least 0.2 ng/mL after prostatectomy or at least 2 ng/mL above nadir after radiotherapy (median baseline PSA, 0.8 ng/mL; range, 0.2-98.4 ng/mL) underwent ~18F-DCFPyL PET/CT scanning. The primary end point was the correct localization rate.
that's not true," he said. "It cannot identify
A lot of times I see PSMA PET equated to
CT scanning does not replace a microscope.
95% to 98%," he said. 

"It's important for our patients to under-
stand where the value of this test would be," 
Srinivas said. "The biggest thing I see in my
practice is patients with biochemical recur-
rence with the lowest PSA who can do salvage
radiation or metastatic-directed therapy.
To me, that's the biggest value that PSMA
brings to the field."

**PSMA-targeted PET/CT practical considerations**

Tagawa noted that PSMA-targeted imaging
currently has 3 key uses in clinical practice:
(1) deciding on initial treatments, as it can
help identify sites of disease outside the pros-
tate; (2) helping to determine where elevated
PSA levels are coming from; and (3) enabling
optimization of treatment for patients with
metastatic disease by opening the door to use
of PSMA-targeted radionuclide therapy. He
explained that although there are some clear
differences in radiochemistry between the 2
FDA-approved imaging agents, these differ-
ences do not really matter for the end user
because the data for the 2 agents have shown
similar findings. "When compared with the
microscope, each one was approximately 40%.
But when we look at the larger results, in
terms of true positivity, then we're looking at
95% to 98%," he said.

Koo agreed with Tagawa that PSMA PET/
CT scanning does not replace a microscope.
"A lot of times I see PSMA PET equated to
identifying micrometastatic disease, and
that's not true," he said. "It cannot identify
micrometastatic disease. By definition these
are things that we're detecting with a micro-
scope, pathology, and tissue. That's important
because it sheds light on the limitations of
this imaging modality."

Morgans also pointed out that PSMA-based
imaging can only identify PSMA-positive
disease. "Some disease can sometimes be
FDG [fluorodeoxyglucose] avid but not PSMA
avid," she said, emphasizing the importance of
explaining this to patients so that they are
not under the false impression that PSMA
PET/CT imaging will pick up any cancer they
have. Despite its limitations, Morgans said
that "any PSMA PET imaging that [patients]
can undergo is great."

**PROGRESS IN DEVELOPING THERANOSTICS**

"I heard a talk once that [described] our ability
to target PSMA with imaging as a light bulb and our ability to target it with ther-
anostics as a little bomb—and to think
about PSMA being utilized in both ways,
allowing us to image our patients poten-
tially more sensitively or accurately, as
well as potentially [delivering treatment] to
them," Morgans said.

Although no PSMA-based treatments have
yet been approved by the FDA, the radiopharmaceutical lutetium 177 (\(^{177}\text{Lu}\)PSMA-617 has recently been shown to improve progression-free survival (PFS) and overall survival (OS) in men with meta-
static CRPC enrolled in the VISION trial
(NCT03511664).\(^{12}\) All patients in the trial
(N = 831) were previously treated with at
least 1 AR-pathway inhibitor and 1 or 2
taxane regimens; thus, this is a popula-
tion with few remaining treatment options
and great unmet need.\(^{12}\) PSMA positivity
was required for inclusion in the study
and was determined via \(^{68}\text{Ga}\) PSMA-11
PET/CT scanning.

\(^{177}\text{Lu}\)-PSMA-617 is a radioligand designed
to deliver \(\beta\)-particle radiation to PSMA-
expressing cells and their surrounding
microenvironment. In the VISION trial,
patients were randomly assigned 2:1 to
receive \(^{177}\text{Lu}\)-PSMA-617 (7.4 GBq every 6
weeks for 4-6 cycles) plus protocol-permit-
ted standard care (n = 551) or standard care
alone (n = 280). Protocol-permitted standard
care did not allow use of chemotherapy,
immunotherapy, radium-223 dichloride
(Xofigo), or investigational drugs.

| TABLE. VISION Trial Primary and Secondary Efficacy Findings\(^{12}\) |  |
|---|---|---|
| **Primary end points** | \(^{177}\text{Lu}\)-PSMA-617 + standard care (n = 385)* | Standard care (n = 196) |
| Median PFS, months | 8.7 | 3.4 |
| HR for progression or death (99.2% CI); \(P\) value | 0.40 (0.29-0.57); \(P < .001\) |  |
| Median OS, months | 15.3 | 11.3 |
| HR for death (95% CI); \(P\) value | 0.62 (0.52-0.74); \(P < .001\) |  |
| **Secondary end points** |  |
| Time to first symptomatic skeletal event, months | 11.5 | 6.8 |
| HR (95% CI); \(P\) value | 0.50 (0.40-0.62); \(P < .001\) |  |
| **Objective response** | \(^{177}\text{Lu}\)-PSMA-617 + standard care (n = 184)* | Standard care (n = 64) |
| CR, n (%)* | 17 (9.2) | 0 (0) |
| PR, n (%) | 77 (41.8) | 2 (3.0) |

*CR and PR data were determined for the 248 patients who had measurable target lesions according to RECIST 1.1, based on independent central review at baseline.

CR, complete response; \(^{177}\text{Lu}\), lutetium 177; OS, overall survival; PFS, progression-free survival; PR, partial response.
After a median follow-up of 20.9 months, PSMA-directed radiotherapy plus the standard of care significantly prolonged imaging-based PFS and OS vs standard care alone (TABLE). Additionally, the key secondary endpoints, including time to symptomatic skeletal events and objective response, favored the addition of 177Lu-PSMA-617.

“The disappointing part was that the overall effect was not as huge as what we might have wanted. But it was in keeping with all of the drugs that we have had in the CRPC space, with an absolute improvement in the efficacy of the drugs that we have had in the CRPC setting, but we are awaiting the FDA label to see what the indication will be.”

The incidence of adverse effects (AEs) grade 3 or higher was more prevalent in the 177Lu-PSMA-617 arm vs the standard-of-care arm, occurring in 52.7% and 38.0% of patients, respectively. The most common AEs with PSMA-directed treatment included fatigue, dry mouth, nausea, and anemia, with most of these being grade 1 or 2. Five AEs that led to death were attributed to 177Lu-PSMA-617: pancytopenia (n = 2), bone marrow failure (n = 1), subdural hematoma (n = 1), and intracranial hemorrhage (n = 1).

“Overall, it’s very well tolerated…better tolerated than chemotherapy in a head-to-head setting, except for a few items, such as dry mouth and thrombocytopenia,” Tagawa said, referring to the AEs observed in the TheraP trial (NCT03392428). In this study, grade 3 to 4 AEs occurred in 32 of 98 men (33%) in the 177Lu-PSMA-617 arm vs 45 of 85 men (53%) in the cabazitaxel (Jevtana) arm. No deaths were attributed to 177Lu-PSMA-617.

Tagawa noted that several 177Lu-PSMA-617 trials are ongoing and recruiting patients, including those in earlier treatment settings. “I think many more patients, particularly those who are lucky to have it locally or are able to travel a little bit, will have opportunities to receive 177Lu-PSMA-617,” he said.

**REFERENCES**

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