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CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

Complex mechanisms of estrogen receptor (ER) signaling have been associated with tumor growth.\textsuperscript{1-3}
In ER+/HER2– mBC, the ER pathways are involved in tumor progression and treatment escape mechanisms that enable endocrine resistance.\textsuperscript{1,2,4,5}

To strengthen the fight against resistance, could advancements in ER antagonism and degradation help decrease the ER pathway’s downstream effects?

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Metastatic Breast Cancer Enters a New Era of HER2 Classification

by ANDREW SMITH

Following a standing ovation for data from DESTINY-Breast04 presented at the 2022 American Society of Clinical Oncology Annual Meeting, HER2 classification has generated buzz for clinicians and pathologists. Experts discuss the new era of stratification dawning for patients with breast cancer and beyond.

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TOC, CONTINUED ON PAGE 11
**MONJUVI®**

*tafasitamab-cxix* | *200mg*

*for injection, for intravenous use*

**MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant**

**INDICATIONS & USAGE**

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

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

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend tfasitamab-cxix (MONJUVI)**

in combination with lenalidomide as a second-line or subsequent therapy option for DLBCL in patients who are not candidates for transplant.\(^2\)*

\(^1\)It is unclear if tafasitamab or loncastuximab tesirine or if any other CD-19 directed therapy would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.

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.

DLBCL=diffuse large B-cell lymphoma; NCCN=National Comprehensive Cancer Network.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**

None.

**Warnings and Precautions**

**Infusion-Related Reactions**

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

**Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.**
MONJUVI is second-line targeted immunotherapy for 
adult patients with DLBCL who are ineligible for transplant

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

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

L-MIND study design

- L-MIND was an open-label, multicenter, single-arm study that evaluated the efficacy and safety of MONJUVI in combination with lenalidomide followed by MONJUVI monotherapy in adult patients with R/R DLBCL after 1 to 3 prior systemic DLBCL therapies, including CD20-containing therapy. The median number of prior therapies was 2
- Enrolled patients at the time of the trial were not eligible for or refused ASCT
- Efficacy was established in 71 patients with DLBCL (confirmed by central laboratory) based on best ORR (defined as the proportion of complete and partial responders) and DoR, as assessed by an Independent Review Committee using the International Working Group Response Criteria (Cheson 2007)
- Patients received MONJUVI 12 mg/kg intravenously in combination with lenalidomide (25 mg orally on days 1 to 21 of each 28-day cycle) for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont’d)

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

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

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

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

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

Please see additional Important Safety Information and the Brief Summary of Prescribing Information on the following pages.
1-YEAR PRIMARY ANALYSIS

**HIGH ORR REACHED**, with a majority of responders achieving CR

1-year primary analysis in patients with R/R DLBCL (N=71)

| Best ORR: 55% (n=39; 95% CI: 43%, 67%) |
| CR: 37% | PR: 18% |

**SUSTAINED REMISSION** in patients with R/R DLBCL

1-year primary analysis in patients with R/R DLBCL (N=71)

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

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3-YEAR FOLLOW-UP ANALYSIS

MONJUVI, in combination with lenalidomide, was granted accelerated approval based on the 1-year primary analysis of the L-MIND study. The data for the 3-year analysis of the L-MIND study has not yet been submitted to or reviewed by the FDA. The status with respect to potential inclusion of these data in the final, FDA-approved labeling has yet to be determined.

1This analysis is exploratory in nature, and L-MIND was not designed or powered to evaluate and compare multiple subgroups. These results should be interpreted with caution given the small sample size, which may lead to estimates that are unstable.

2Assessed by an Independent Review Committee.1,3

3Kaplan-Meier estimates.1,3

4Due to rounding, ORR percentages may not correspond with the sum of CR and PR percentages.

5The cutoff date for the primary analysis was November 30, 2018 and occurred after the last patient enrolled had completed 12 months of follow-up. The cutoff date for the 3-year follow-up analysis was October 30, 2020 and occurred after the last patient enrolled had completed 35 months of follow-up.3,4

R/R=relapsed/refractory; ASCT=autologous stem cell transplant; ORR=best overall response rate; DoR=duration of response; CR=complete response rate; CI=confidence interval; PR=partial response rate; NR=not reached.

---

**ORR (3-year analysis)**

3-year follow-up analysis in patients with R/R DLBCL (N=71)

| Best ORR: 54% (n=38; 95% CI: 41%, 66%) |
| CR: 35% | PR: 18% |

**Response rates in 2L and 3L+ (3-year analysis)**

3-year follow-up analysis in patients with R/R DLBCL (N=71)

- 2L (n=35)
  - 43% CR
  - 20% PR

- 3L+ (n=36)
  - 63% ORR (n=22; 95% CI: 45%, 79%)
  - 28% CR
  - 17% PR
  - 44% ORR (n=16; 95% CI: 28%, 62%)

**Median DoR (3-year analysis)**

3-year follow-up analysis in patients with R/R DLBCL (N=71)

Median DoR: 43.9 months (95% CI: 15.0, NR)

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REACH FOR MONJUVI

MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant.

INDICATIONS & USAGE
MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT). This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION
Warnings and Precautions (cont’d)

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

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

Adverse Reactions
Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥6% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

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

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

The most common adverse reactions (≥20%) were neutropenia (51%), fatigue (38%), anemia (36%), diarrhea (36%), thrombocytopenia (31%), cough (26%), pyrexia (24%), peripheral edema (24%), respiratory tract infection (24%), and decreased appetite (22%).

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

To learn more, visit MonjuiHCP.com

For information about patient assistance, visit MyMISSIONSupport.com

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

MONJUVI® (tafasitamab-cxix)
Initial U.S. Approval: 2020

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

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

CONTRAINDICATIONS
None.

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

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12%, and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 27% of patients. Monitor CBC prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony-stimulating factor administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections
Fatal and/or serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose. In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 25.5% of the 81 patients. Monitor patients for signs and symptoms of infection and manage infections as appropriate.

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

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

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
The safety of MONJUVI was evaluated in L-MIND. Patients (N=81) received MONJUVI 12 mg/kg intravenously in combination with lenalidomide for a maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:
- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Among patients who received MONJUVI, 57% were exposed for 6 months or longer, 42% were exposed for greater than one year, and 24% were exposed for greater than two years.

Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in 36% of patients included infections (26%), including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%). Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15% of the most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

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

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

Table 3 summarizes the adverse reactions in L-MIND.

<table>
<thead>
<tr>
<th>MONJUVI (N=81)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection†</td>
<td>24</td>
<td>4.9</td>
</tr>
<tr>
<td>Urinary tract infection†</td>
<td>17</td>
<td>4.9</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>19</td>
<td>2.5</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash‡</td>
<td>12</td>
<td>2.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

†Fatigue includes asthenia and fatigue
‡Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection
+Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal

Abdominal pain includes abdominal pain, abdominal pain lower, and abdominal pain upper.

‡Rash includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash pustular

Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:
- Blood and lymphatic system disorders: lymphopenia (6%)
- General disorders and administration site conditions: infusion-related reaction (6%)
- Infections: sepsis (4.9%)
- Investigations: weight decreased (4.9%)
- Musculoskeletal and connective tissue disorders: arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- Neoplasms benign, malignant and unspecified: basal cell carcinoma (1.2%)
- Nervous system disorders: headache (9%), paresthesia (7%), dyseusia (6%)
- Respiratory, thoracic and mediastinal disorders: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- Skin and subcutaneous tissue disorders: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)
Table 4 summarizes the laboratory abnormalities in L-MIND.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Gamma glutamyl transferase increased</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time increased</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

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

**Immunogenicity**

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

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

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

**Clinical Considerations**

**Fetuses/Neonatal Adverse Reactions**

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

**Data**

**Animal Data**

Animal reproductive studies have not been conducted with tafasitamab-cxix.

Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

**Lactation**

**Risk Summary**

There are no data on the presence of tafasitamab-cxix in human milk or the effects on the breastfed child or milk production. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to MONJUVI are unknown. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose. Refer to lenalidomide prescribing information for additional information.
Mutation Classification Reshapes Treatment Practices in 2022 and Beyond

RECENT APPROVALS FOR HER2-TARGETED agents have reshaped clinical practice standards with fam-trastuzumab deruxtecan-nxki (Enhertu) being the most notable and talked about agent in lung and breast cancers. Data seen for notably hard-to-treat populations and unique subgroups of patients have necessitated closer relationships between oncologists and pathologists.

In breast cancer, Erika P. Hamilton, MD, noted in a presentation during the 23rd Annual International Congress of the Future of Breast Cancer West that a new language may be needed for HER2 classification. “What we traditionally classify as HER2-low is not HER2 0 and it is not what’s traditionally considered HER2 positive—[immunohistochemistry] IHC 3+,” Hamilton said. In our cover story, leading breast oncologists discuss how the approval of trastuzumab deruxtecan is redefining how HER2-low disease is used to stratify patients in clinical practice. Hamilton noted that this starts with medical oncologists changing the way HER2 status is communicated. “Many pathologists will tell you that they quickly look at a slide and pull it off if they don’t see that the patient is HER2 positive. [As a result] we may be getting a lot of 0 results that aren’t actually 0s. They just know that they’re not positive. If you move around with a little bit of tumor heterogeneity, I think that we’re probably going to see even more patients [who] have at least an IHC 1+,” Hamilton said. She added that and that although definitions are still being parsed out across clinics, wording in notes will matter now that HER2-low disease is actionable.

A different story is being told in lung cancer with HER2 mutations just making their entrance into the treatment landscape as an actionable target. Rare among patients with non–small cell lung cancer (NSCLC), HER2 mutations occurrs in approximately 3% of adenocarcinomas, mostly in the form of exon 20 in-frame insertions. Consistant efficacy findings have eluded investigators with HER2-targeted approaches including ado-trastuzumab emtansine (T-DM1; Kadcyla) having divergent results. However, the approval of trastuzumab deruxtecan, with responses observed in close to 60% of patients.

In our Drug Spotlight, Bejamin P. Levy, MD, notes, “The approval of [trastuzumab deruxtecan] will underscore the importance of molecular testing; we cannot give this drug or other drugs [like it] unless we identify the alteration.”

This trend of classification and testing is ripe for discussion and will be incorporated into several sessions planned for upcoming meetings from Physicians’ Education Resource® such as the 20th Annual School of Breast Oncology® meeting in October and the 17th Annual New York Lung Cancers Symposium® in November. To learn more about these meetings, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®

REFERENCES
Implementation Research Takes On an Increasingly Essential Role in Oncology

by MAURIE MARKMAN, MD

CLINICAL TRIALS PLAY a central role in oncology. The existence of solid, evidence-based disease management would not be possible without the conduct of well-designed and well-conducted studies.

However, the publication of the objectively meaningful outcomes of such efforts in high-impact peer-reviewed medical journals does not necessarily result in the observations being implemented into routine clinical care. Several reasons may explain the substantial delays noted between the publication of highly relevant data and uptake of the results into practice.

Reasons include the following:
• The results alter well-established, widely accepted approaches to disease treatment.
• Changes may lead to potentially complex, unproductive, and expensive training for clinicians and staff.
• Changes may add time to a routine clinical encounter without adding renumeration.
• There may be a lack of local resources or supportive personnel to implement a new practice.
• Implementation may negatively affect personal and practice finances.

Conversely, if essential training is provided by a source outside the practice on the evidence-based treatment approach, effectively marketed clinical trial results that suggest a new approach to disease management may lead to a greater willingness to carefully evaluate and subsequently employ the tactic. Further, if such implementation is associated with a favorable financial return, a practice will almost certainly show more interest.

If a new anticancer agent demonstrates meaningful activity for new clinical indications in initial registration trials or in subsequent studies leading to regulatory approval, a drug manufacturer may be willing to spend considerable time (and money) to inform oncologists of this development. This may include providing assistance in obtaining third-party insurance coverage for individual patients or any required training related to drug administration and safety.

However, the situation is likely to be quite different if the trial is not associated with a sponsor or any other form of support necessary to optimize meaningful implementation. In the opinion of this commentator, an increasing number of critically relevant observations and important study results published in peer-reviewed medical and oncology literature stagnate because there is no implementation plan or subsequent effort at encouraging clinical uptake.

Investigators of such projects may win awards for the quality of their research, subsequently obtain precious peer-reviewed grant funding, achieve promotion at their institution or elsewhere, or be awarded membership in prestigious national organizations, but their research findings themselves sometimes go nowhere. To be clear, there is no suggestion that this was ever the investigator’s intent, but it may be the result of the absence of an effective implementation plan.

There is a critical need in the oncology community for meaningful, focused efforts in implementation research. Consider the following: A recent study looked at adherence to established guidelines for venous thromboembolism prophylaxis following pancreatic surgery. The study’s
results revealed that among 888 patients deemed eligible to receive such therapy upon hospital discharge, only 3.8% (34 individuals) “filled a prescription for venous thrombotic prophylaxis within 5 days of hospital discharge.” This is rather concerning considering that data from both clinical guidelines and trials support the use of such prophylaxis after major surgery involving the abdominal cavity.2,3

How might surgeons be encouraged to use and inform patients of a known effective and safe measure to reduce the risk of this serious surgery complication?

A second example within the realm of cancer surgery suggests the need to understand and positively affect findings from thoracic oncology studies. A specific example is a retrospective cohort analysis of individuals with stage IB to IIA non–small cell lung cancer (NSCLC) in the ALCHEMIST Screening Trial (NCT02194738) who did not subsequently participate in an adjuvant therapy trial and who had a cancer measuring at least 4 cm in diameter, with or without positive lymph nodes.4

Among 2833 patients (53% women), 95% had surgical resection, but only 53% were found to have had “adequate lymph node dissection.”4 A similarly low percentage of individuals (57%) received any adjuvant therapy, with only 44% receiving a minimum of 4 cycles of platinum-based chemotherapy, despite solid evidence revealing the value of such treatment. Although the authors of this provocative and concerning analysis appropriately conclude that “efforts are needed to optimize the use of proven therapies for early-stage NSCLC”4 the question is how do we effectively implement efforts to change what for many oncologists appears to be current routine surgical practice?5

It is not difficult to find documented evidence outside the realm of surgical oncology that challenges the oncology community to focus research on strategies to more effectively deliver care with documented evidence to improve outcomes or enhance patients’ quality of life. Topics highlighted in recent publications include disparities in electronic screening for cancer-related psychosocial distress6 and inadequacies in performance guideline–recommended geriatric assessments.6

In the opinion of this commentator, there must be a more prominent role in our community’s investigative agenda for implementation research designed to discover and activate strategies to effectively encourage widespread use of new, effective approaches to cancer management.

REFERENCES

INSIDE THE PRACTICE™
Lowe Goes Inside Cleveland Clinic’s 7T MRI Machine

Cleveland Clinic has been at the forefront of advanced imaging as having been one of a handful of sites worldwide to have a 7-Tesla (7T) MRI scanner, which was installed in 2014 for research purposes. After the FDA approved the scanner for clinical use in 2017, the institution upgraded its machine, explained Mark J. Lowe, PhD, director of high field MRI and section head of Imaging Sciences Section at the Imaging Institute at Cleveland Clinic. Compared with 3T MRIs, the 7T scanner has a stronger magnet and therefore can offer clinicians more precise tumor locations, which is especially important for brain tumors.

TO WATCH, VISIT bit.ly/3AxgY15.

AFTER HOURS™
Braunstein Rolls Out His Latest Recipe

Marc J. Braunstein, MD, PhD, discusses how an observation by his thesis adviser in graduate school led to a passion for baking. “She realized I hadn’t gone thoroughly through the protocols in advance and read them and tested them in my head to see what wouldn’t work,” said Braunstein, an assistant professor in the Department of Medicine at NYU Long Island School of Medicine. Taking advice from a friend, Braunstein started baking as an extracurricular experiment. In this episode of After Hours™, he talks through preparing his latest recipe, matcha madeleine cookies.

TO WATCH, VISIT bit.ly/3wfK4zA.

WELLBEING CHECKUP™
Wolfson Discusses the Importance of Building Trust in Health Care

Employers seeking to address health equity, social determinants of health, and other issues that have grown in national discussion amid the pandemic should start with building trust. Daniel Wolfson, executive vice president of the American Board of Internal Medicine Foundation, discusses the importance of trust and how it can promote cost-effective, preventive care. “Trust is foundational to all relationships and health care is about relationships,” Wolfson said. “We see the importance in not just the patient-physician relationship, but in organizational trust, which has really taken a toll during the pandemic.”

TO WATCH, VISIT bit.ly/3QMB90u.
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Trastuzumab Deruxtecan Receives Indications for HER2-Mutant Breast Cancer and NSCLC

The antibody-drug conjugate fam-trastuzumab deruxtecan-nxki (Enhertu) was granted regular and accelerated approvals from the FDA for 2 indications: patients with unresectable or metastatic HER2-low breast cancer and patients with HER2-mutant non–small cell lung cancer (NSCLC).

Approval for patients with HER2-low metastatic breast cancer was supported by findings from the phase 3 DESTINY-Breast04 trial (NCT03734029). Low expression of HER2 was defined as an immunohistochemistry score of 1+ or 2+ with a negative in situ hybridization test. Patients with hormone receptor–positive, HER2-low disease served as the primary end point population. The median progression-free survival was 9.9 months (95% CI, 9.0-11.3) with trastuzumab deruxtecan compared with 5.1 months (95% CI, 4.2-6.8) with chemotherapy (HR, 0.50; 95% CI, 0.40-0.63). The median overall survival was 23.4 months (95% CI, 20.0-24.8) vs 16.8 months (95% CI, 14.5-20.0).

The indication for patients with HER2-mutant unresectable or metastatic NSCLC was supported by data from the phase 2 DESTINY-Lung02 trial (NCT04644237), which evaluated the agent at a dose of 5.4 mg/kg every 3 weeks. Among 52 patients, the confirmed objective response rate was 57.7% (95% CI, 43.2%-71.3%) with a complete response rate of 1.9%. The median duration of response was 8.7 months (95% CI, 7.1-not estimable). Continued approval of this indication is contingent on additional results.

Capmatinib Gets Stamp of Approval for Metastatic NSCLC

The FDA has granted regular approval to capmatinib (Tabrecta) for the treatment of adult patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have a mutation leading to MET exon 14 skipping. The approval comes after capmatinib received accelerated approval on May 6, 2020, for the same indication based on the multicenter, open-label, multicohort phase 2 GEOMETRY Mono-1 trial (NCT02414139). The updated analysis was conducted with 63 additional patients and an additional 22 months of follow-up. Among 60 treatment-naïve patients, the overall response rate (ORR) of 68% (95% CI, 55%-80%) with a median duration of response (DOR) of 16.6 months (95% CI, 8.4-22.1). One hundred previously treated patients had an ORR of 44% (95% CI, 34%-54%) with a median DOR of 9.7 months (95% CI, 5.6-13). The disease control rates in the treatment-naïve and pretreated patients were 78.3% (95% CI, 66.7%-87.3%) and 96.4% (95% CI, 81.7%-99.9%), respectively.

Darolutamide Plus Docetaxel Gets Go-ahead for Metastatic Hormone-Sensitive Prostate Cancer

The tablet formulation of darolutamide (Nubeqa) in combination with docetaxel has been approved by the FDA for the treatment of adult patients with metastatic hormone-sensitive prostate cancer. Data from the phase 3 ARASENS trial (NCT02799602), which compared the efficacy of darolutamide plus docetaxel with docetaxel alone, supported the approval. The median overall survival with the combination was not reached (NR; 95% CI, NR-NR) compared with 48.9 months (95% CI, 44.4-NR) with darolutamide alone (HR, 0.68; 95% CI, 0.57-0.80; P < .0001). The median time-to-pain progression was significantly delayed in patients treated with darolutamide plus docetaxel (HR, 0.79; 95% CI, 0.66-0.95; 1-sided P = .006). Patients received intravenous docetaxel at 75 mg/m2 every 3 weeks for up to 6 cycles with or without 600 mg of oral darolutamide twice daily. All patients received androgen deprivation therapy concurrently or underwent a bilateral orchietomy.

Omidubicel Moves Ahead for Blood Cancers Requiring Transplant

The biologics license application for omidubicel for patients with blood cancer in need of allogeneic hematopoietic stem cell transplant has been accepted for priority review by the FDA. The anticipated decision date is January 30, 2023. Omidubicel is a stem/progenitor cell–based product composed of ex vivo expanded allogeneic cells from 1 unit of umbilical cord blood.

Data from a phase 3 trial (NCT02730299) showed that patients who received omidubicel (n = 52) had a median time to neutrophil engraftment of 12 days (95% CI, 10-14) vs 22 days (95% CI, 19-25) with a standard umbilical cord blood graft (n = 55; P <.001). By day 42 following transplantation, the cumulative incidence of neutrophil engraftment was 96% with a median of 10 days to onset (95% CI, 8-13) in the omidubicel arm and 89% with a median of 20 days to onset (95% CI, 19-24) in the control arm (P <.001).
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Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

To nominate, please visit: giantsofcancercare.com/nominate

PROGRAM OVERVIEW

- Nominations are open through January 31, 2023.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection committee of more than 120 oncologists will vote to determine the 2023 inductees.
- The 2023 Giants of Cancer Care® class will be announced in spring 2023.

Abbreviated Rules: NO PURCHASE NECESSARY. Contest begins on or about June 2, 2022 and ends on Tuesday, January 31, 2023 at 11:59 p.m. ET (“Contest Period”), with the option to extend the nomination period through February 28, 2023. Open only to those who are 18 years of age or older at the time of entry and who are a licensed healthcare professional (i.e., MD, DO, PhD, and/or RN) working in the oncology space at the time of application and award. Subject to Official Rules. See Official Rules at www.giantsofcancercare.com for additional eligibility restrictions, prize descriptions, restrictions, and complete details. Odds of winning depend on the number of eligible entries received. Void where prohibited. Sponsor: Intellisphere, LLC.
Drug Spotlight

DAROLUTAMIDE (NUBEQA)

Darolutamide Tablets Usher in New Standard of Care in mHSPC

by MEGAN HOLLASCH

THE APPROVAL OF THE triplet regimen of darolutamide (Nubeqa) tablets with docetaxel in addition to androgen deprivation therapy (ADT) has shifted the treatment paradigm for patients with metastatic hormone-sensitive prostate cancer (mHSPC).1

Results from the phase 3 ARASENS trial (NCT02799602), which evaluated the safety and efficacy of ADT plus docetaxel and the androgen receptor (AR) inhibitor darolutamide vs ADT plus docetaxel, supported the approval. The median overall survival (OS) was not reached (NR; 95% CI, NR-NR) in the darolutamide plus docetaxel arm compared with 48.9 months (95% CI; 44.4-NR) in the docetaxel plus placebo arm (HR, 0.68; 95% CI, 0.57-0.80; P < .0001). The darolutamide combination also resulted in a statistically significant delay in time-to-pain progression (HR, 0.79; 95% CI, 0.66-0.95; 1-sided P = .006).

“The trial demonstrated that the triplet therapy improved upon a current standard of care or prior standard of care, which was ADT plus docetaxel alone,” Jacob Berchuck, MD, said. “In my mind, consistent with the FDA approval, the triplet of ADT, docetaxel, and darolutamide is the new standard of care for the first-line treatment for men with mHSPC.”

In an interview with OncologyLive®, Berchuck, a medical oncologist in the Lank Center for Genitourinary Oncology at Dana-Farber/Brigham and Women’s Cancer Center, in Boston, Massachusetts, further discussed the effect of the approval on the standard of care for patients with mHSPC.

How do you see the approval of this combination affecting current practice patterns?

Men with mHSPC have several treatment options based on randomized prospective data that demonstrated that intensifying first-line treatment beyond ADT by adding either docetaxel or a potent AR inhibitor improves OS when used in the first-line setting. ARASENS [evaluated] whether the triplet regimen improves outcomes relative to ADT and docetaxel plus placebo. The [triplet] improved OS for patients with mHSPC relative to ADT and docetaxel. This is the first FDA approval specifically for triplet therapy for the first-line treatment of patients with mHSPC.

The question is: Which patients are going to benefit from triplet therapy, [in other words, which] patients need triplet therapy? ARASENS did not completely answer this, [but], for most patients, ADT plus an AR signaling inhibitor such as darolutamide, enzalutamide [Xtandi], or apalutamide [Erleada] is the preferred option.

ADT plus docetaxel in my clinic is reserved for patients with high-volume mHSPC. That is a subset of [approximately] one-third of men with metastatic prostate cancer, but I reserve chemotherapy for that subset.

In most patients, I prefer an AR pathway inhibitor. The design of ARASENS doesn’t answer [whether] adding chemotherapy to ADT plus an AR inhibitor improves upon ADT and the AR inhibitor alone. The way that I’m using these data and the FDA approval in my clinic [starts with asking] if [the patient is] fit for chemotherapy. If the answer is no, then I am not going to be using this triplet therapy and will favor an ADT plus AR inhibitor.

For patients who are chemotherapy fit, I ask: Is there compelling evidence that chemotherapy is going to benefit this patient? What we know from the charted data is that this benefit [seems] to be most pronounced in men with high-volume disease. If a patient has high-volume disease, and I think that they are chemotherapy fit and are likely to benefit, those are the patients I am treating with the triplet therapy.

For patients who are not chemotherapy fit or have low-volume mHSPC, I am still favoring ADT with an AR inhibitor. Other factors [are also considered such as] age, comorbidity, etc. The data are going to evolve to identify which patients are most likely to benefit from the triplet therapy as opposed to the standard doublet regimen.

Could you go into detail about the pivotal efficacy data from ARASENS?

Patients were randomly assigned to receive ADT and docetaxel for 6 cycles and to receive darolutamide 600 mg, twice [daily] or placebo. The primary end point was OS and men in the darolutamide arm had a 32% reduction in the risk of [death] during the study period. Two of the key secondary end points were time to castration resistance and time to pain progression, which both significantly favored the addition of darolutamide to ADT plus docetaxel.

We [saw a clear] improvement on a standard of care in terms of efficacy, with very little in the way of toxicity. All these results [show] that this is a new standard of care for men with mHSPC.

Are there patients with contraindications for whom you would not recommend this regimen?

There really are not. What is exciting about this approval and the expanded opportunity to use darolutamide is that it is a very well-tolerated drug.

[Darolutamide] is an AR inhibitor that was specifically designed to have 2 favorable features. It has very little crossing of the blood-brain barrier, so the cognitive and neurologic adverse effects of AR inhibition are minimized with darolutamide relative to other AR inhibitors. Second, it has very few clinical drug interactions, and it is a favorable drug when we think about using it in combination with other treatments such as ADT and docetaxel. Those features make it a very safe drug to use for most patients.

What does the future hold for this patient population?

The big unanswered question in my mind is: Which patients are candidates for and benefit from adding docetaxel to those drugs [ADT plus an AR inhibitor]? We do not have that answer from ARASENS. The short answer is that darolutamide is well tolerated and had very little toxicity beyond ADT and docetaxel alone.

In addition to ARASENS, there was a very similar study that was reported at [the European Society of Medical Oncology Congress 2021]. The [phase 3] PEACE-1 study [NCT01957436] looked at a similar question of adding abiraterone [Zytiga] to ADT and docetaxel. The study’s results were very similar, [with] improvement when adding the AR signaling inhibitor abiraterone[to] ADT and docetaxel.

REFERENCES


**Drug Spotlight**

**BASELINE PATIENT CHARACTERISTICS**

**Median age (years, range)**

<table>
<thead>
<tr>
<th>Darolutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>67</strong> (41-89)</td>
<td><strong>67</strong> (42-86)</td>
</tr>
</tbody>
</table>

| N | 651 | 654 |

**DAROLUTAMIDE**

**PLACEBO**

**Metastasis stage at initial diagnosis**

- **DAROLUTAMIDE**
  - M1: 85.7%
  - M0: 13.2%

- **PLACEBO**
  - M1: 86.5%
  - M0: 12.5%

**Initial diagnosis of metastatic disease**

- **DAROLUTAMIDE**
  - 3.5%

- **PLACEBO**
  - 2.4%

**Baseline PSA level**

- **Darolutamide**
  - Median serum PSA level (range): 30.3 ng/mL (0-9219)

- **Placebo**
  - Median serum PSA level (range): 24.2 ng/mL (0-11,947)

**REFERENCES**


**PIVOTAL CLINICAL TRIAL**

ARASENS (NCT02799602) was a multicenter, double-blind, placebo-controlled clinical trial evaluating darolutamide tablets with docetaxel vs placebo plus docetaxel in patients with mHSPC. All patients received androgen deprivation therapy.

**EFFICACY RESULTS IN ARASENS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Darolutamide plus docetaxel (n = 651)</th>
<th>Docetaxel (n = 654)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NR-NR)</td>
<td>NR (NR-NR)</td>
</tr>
<tr>
<td>Time to pain progression</td>
<td>HR, 0.68 (0.57-0.80) P &lt; .0001</td>
<td>HR, 0.79; 95% CI, 0.66-0.95; 1-sided P = .006</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

- Ischemic heart disease
- Seizure
- Embryo-fetal toxicity

**COMMONLY REPORTED ADVERSE EFFECTS IN ARASENS**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Darolutamide plus docetaxel (n = 652)</th>
<th>Docetaxel (n = 650)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
</tr>
<tr>
<td>Constipation</td>
<td>23%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Rash</td>
<td>19%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>18%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Weight increase</td>
<td>18%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Mechanism of Action**

Darolutamide is an androgen receptor (AR) inhibitor that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription.

**How Supplied**

300-mg film-coated tablets for oral use

**Dosing**

- 600 mg taken with food, orally, twice daily
- Patients should also receive a gonadotropin-releasing hormone analogue concurrently or have had bilateral orchiectomy.

**FDA Approval: August 5, 2022**

FDA grants approval to darolutamide (Nubeqa) tablets in combination with docetaxel for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC).

**Company:** Bayer HealthCare Pharmaceuticals Inc
**Drug Spotlight**

**FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU)**

**Trastuzumab Deruxtecan Expands the Targeted Landscape for HER2-Mutant NSCLC**

**by MEGAN HOLLASCH**

THE ANTIBODY-DRUG CONJUGATE (ADC) fam-trastuzumab deruxtecan-nxi (Enhertu) is breaking new ground in the treatment of non–small cell lung cancer (NSCLC), according to Benjamin P. Levy, MD.

On August 11, 2022, the FDA granted accelerated approval to trastuzumab deruxtecan for the treatment of patients with unresectable or metastatic NSCLC who have received a prior systemic therapy and whose tumors have activating HER2 mutations.¹

Results from the phase 2 DESTINY-Lung02 trial (NCT04644237), which evaluated the safety and efficacy of trastuzumab deruxtecan in patients with metastatic NSCLC harboring a HER2 mutation, supported the approval. Among 52 efficacy-evaluable patients the objective response rate (ORR) was 57.7% (95% CI, 43.2%-71.3%), including a 1.9% complete response rate. Additionally, the median duration of response (DOR) was 8.7 months (95% CI, 7.1–not estimable [NE]).²

“This [approval] is exciting. It is yet another tool in our therapeutic armamentarium to deliver personalized therapy for patients with NSCLC, specifically, patients who have HER2 alterations,” Levy said.

In an interview with OncologyLive®, Levy, the clinical director of medical oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center at Sibley Memorial Hospital and an associate professor of oncology at Johns Hopkins University School of Medicine in Baltimore, Maryland, discussed treatment considerations for the integration of trastuzumab deruxtecan into practice and what this approval signals for the future of the field.

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**Q How does the approval of trastuzumab deruxtecan affect the treatment of HER2-mutant NSCLC?**

Historically, we have not been able to [effectively treat patients with] this alteration and we have a very good drug now, the [ADC] trastuzumab deruxtecan, which can elicit durable and meaningful responses. [This is a] big change. HER2 alterations are now the 10th biomarker in lung adenocarcinoma allowing us to give another targeted therapy.

The approval will underscore the importance of molecular testing; we cannot give this drug or other drugs [like it] unless we identify the alteration. HER2 mutations have not been druggable—we have been giving chemotherapy and potentially even chemotherapy with immunotherapy. We have not had a lot of luck with other tyrosine kinase inhibitors or other monoclonal antibodies, so this is exciting. This also introduces for the first time an ADC into the field of therapeutics for NSCLC. This is going to create a lot of excitement about this class of drugs, and we will see more ADCs come down the pike and be used in everyday practice for patients with lung cancer.

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**Q Given its safety profile, are there certain patients whom you would not treat with trastuzumab deruxtecan?**

I do not believe so. This drug is exceptionally well tolerated. Clearly, when administering it to patients with underlying interstitial lung disease you want to be careful. But I have had experience with this drug. It is reasonably well tolerated. Like any ADC, we need to be mindful of cytopenia, fatigue, and nausea. All in all, this is emblematic of where we are heading in the field, which is that we are getting better therapies that elicit more meaningful responses that are better tolerated.

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**Q What are your thoughts on the companion diagnostic tests, Oncomine Dx Target Test and Guardant360 CDx, that have also been approved by the FDA?**

You cannot give this drug unless you test, and complete testing is predicated on good next-generation sequencing, both in tissue and in liquid. I would encourage everyone to make sure that they are doing both and if we can do both, we are more likely to capture these HER2 alterations and then we can give these drugs.

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**Q What do these data signal about future directions for the field?**

This is a testament to the science; it is a testament to all of the hard work from the physicians, both clinically and translationally, to get a good drug to the patients who have HER2 alterations. It is a testament to precision medicine, to personalized medicine, and—I am biased, but—I [think] lung cancer is the poster child for precision medicine. This is yet another drug that we can use for patients with specific alterations.

Targeted therapies are very important for patients, and I think we’ve just begun to scratch the surface on how we leverage genotype-directed therapies for patients with specific alterations. We’ve got 10 biomarkers. My hope is within 5 years, we’ll have another 5 to 10 biomarkers that we can use that drive decision-making for targeted therapy. I also think that combination approaches are going to be important. Wedding alterations to single-agent drugs is important, but having combination approaches is going to be important to advance the field.

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**REFERENCES**


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**Q Please discuss the pivotal efficacy data from the phase 2 DESTINY-Lung02 trial.**

DESTINY-Lung02 was a multicenter randomized study of trastuzumab deruxtecan in patients with HER2-mutated NSCLC who had prior treatment. [Investigators] were looking at 2 different doses: 5.4 mg/kg every 3 weeks [or] 6.4 mg/kg. The primary end point was ORR.

When [investigators] looked at the 52 patients in the primary efficacy population, for those patients who got 5.4 mg/kg, the ORR was 58% and the DOR was 8.7 months. That is remarkable and this is going to change the way that we treat patients.

Importantly, we can talk about efficacy, but we certainly need to mention tolerability. There were some adverse events noted, including laboratory abnormalities, nausea, decreased white blood cell count. [However], we did not see higher rates of interstitial lung disease. [It is present], but [it] was not as high as we [those seen] in the 6.4-mg/kg dose.

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**Levy on the Approval of Trastuzumab Deruxtecan in HER2-Mutant NSCLC**

Benjamin P. Levy, MD, discusses the historically difficult-to-target HER2 alteration in non–small cell lung cancer and what trastuzumab deruxtecan offers this patient population.

**Watch Now**

bit.ly/3R33e3M
FDA Approval: August 11, 2022
The FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu) for adult patients with unresectable or metastatic non–small cell lung cancer (NSCLC) harboring a HER2 mutation who have received a prior systemic therapy.

Mechanism of Action
Trastuzumab deruxtecan is a humanized anti-HER2 G1 antibody-drug conjugate. The small molecule, DXd, is a topoisomerase I inhibitor attached to the antibody by a cleavable linker.

How Supplied
100 mg of lyophilized powder in a single-dose vial

PIVOTAL CLINICAL TRIAL
DESTINY-Lung02 (NCT04644237) was a multicenter, multicohort, randomized trial of patients with unresectable or metastatic HER2-mutant nonsquamous NSCLC with disease progression after 1 prior systemic therapy. Patients received trastuzumab deruxtecan at 6.4 mg/kg or 5.4 mg/kg. Efficacy for approval was based on the 5.4-mg/kg dose.

Efficacy Results in Destiny-Lung02

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab deruxtecan (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>57.7% (43.2%-71.3%)</td>
</tr>
<tr>
<td>CR</td>
<td>1.9%</td>
</tr>
<tr>
<td>PR</td>
<td>55.8%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>8.7 (7.1-NE)</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; PR, partial response.

Warnings and Precautions
- Neutropenia
- Left ventricular dysfunction

Box Warnings
Interstitial lung disease (ILD)
Monitor for signs and symptoms of ILD and pneumonitis and promptly investigate symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms.
- Permanently discontinue trastuzumab deruxtecan in all patients with grade 2 or higher ILD/pneumonitis.
- Advise patients of the risk and to immediately report symptoms.

Embryo-fetal toxicity
Advise patients of the risk and the need for effective contraception.

Commonly Reported Adverse Effects in Destiny-Lung02

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Trastuzumab deruxtecan (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>61%</td>
</tr>
<tr>
<td>Constipation</td>
<td>31%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26%</td>
</tr>
<tr>
<td>Anemia</td>
<td>34%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30%</td>
</tr>
</tbody>
</table>

References
Adverse reactions occurring more frequently in the NUBEQA arm (≥2% vs placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%). Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

**Indication**

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

**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.

**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.

**Study Design**

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤10 months. 1509 patients were randomized 2:1 to 600 mg NUBEQA twice daily (n=955) or placebo (n=554). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤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. 1,2 ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging.
NUBEQA® (darolutamide) tablets, for oral use

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).

2 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 [see Clinical Pharmacology (12.1)].

Advises females 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 (8.4, 8.5)).

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.

ARANIS, 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 ARANIS study received a concomitant percutaneous-releasing hormone (SrP) analog or had a bilateral orchectomy. The median duration of exposure was 14.4 months (range 0.4 – 43.3 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 hemorrhagic. Overall 3.9% of patients receiving NUBEQA and 3.7% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.1%), cardiac arrhythmia (0.1%), general physical health deterioration (0.1%), and pulmonary embolism (0.1%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA and 8% of patients receiving placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

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

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

Table 1 shows adverse reactions in ARANIS reported in the NUBEQA arm with ≥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 ARANIS study.

Table 1: Adverse Reactions in ARANIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grades ≥ 3</th>
<th>Placebo</th>
<th>Grades ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NUBEQA (n=794)</td>
<td>Placebo (n=554)</td>
<td>NUBEQA (n=794)</td>
<td>Placebo (n=554)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Laboratory Abnormalities in ARANIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>NUBEQA (n=794)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>9</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0.1</td>
<td>14</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on NUBEQA
Combination P-gp and Strong or Moderate CYP3A4 Inhibitor
Concomitant use of NUBEQA with a P-gp and strong or moderate CYP3A4 inhibitor decreases darolutamide exposure which increases NUBEQA activity [see Clinical Pharmacology (12.2)]. Avoid concurrent use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inhibitors.

Combination use of NUBEQA with a P-gp and strong CYP3A4 inhibitor decreases darolutamide exposure which increases NUBEQA activity [see Clinical Pharmacology (12.2)], which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dose and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs
Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptide (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 (12.2)], which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates when possible. It was used together, monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see Clinical Pharmacology (12.2)].

References:

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 toxicology 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
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 (8.4, 8.5)).

Interactions
Males
- Refer to animal studies. NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (12.1)].

8.4 Pediatric Use
Safety and effectiveness of NUBEQA have not been established.

8.5 Geriatric Use
Of the 954 patients who received NUBEQA in ARANIS, 84% of patients were 65 years or over, and 49% were 75 years or older. 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 (2.2) and Clinical Pharmacology (12.2)]. 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 (2.2) and Clinical Pharmacology (12.2)]. 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.

9 OVERDOSAGE
There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg per day, equivalent to a daily dose of 1 900 mg. No dose limiting toxicities were observed with this dose.

Consider the nature and the site of irritation for potential toxicity, and assess the risk of reirritation. At least a 2-point worsening from baseline of pain progression was defined as time from randomization to time of first evidence of progression in clinical trials, as assessed by CT, MRI, or 99mTc bone scan by BICR, unacceptable toxicity, or withdrawal.1,2

OS was a key secondary endpoint.1

Secondary endpoint:

15 MONTHS WITHOUT PAIN PROGRESSION1,3*

Time to pain progression was defined as at least a 2-point worsening from baseline of pain

40.4 months vs 18.4 months

HR: 0.65; 95% CI: 0.53-0.79; <0.0001.

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-

controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time

of 10-25 months. MFS was defined as time from randomization to time of first evidence of

radiographic disease progression, as assessed by CT, MRI, or 99mTc bone scan by BICR, unacceptable toxicity, or withdrawal.1,2

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Metastatic Breast Cancer Enters a New Era of HER2 Classification

by ANDREW SMITH

A DRAMATIC PRESENTATION AT the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting changed treatment standards seemingly overnight for women with previously treated metastatic HER2-low breast cancer. However, fundamental questions remain. What is HER2-low breast cancer? Are low levels of HER2 meaningful drivers of cancer progression? How can oncologists predict which patients will benefit from treatment with the antibody-drug conjugate (ADC) fam-trastuzumab deruxtecan-nxki (Enhertu)?

Investigators of the phase 3 DESTINY-Breast04 trial (NCT03734029) enrolled previously treated patients with HER2-low metastatic breast cancer, which was defined for the trial as a score of 1+ on immunohistochemical (IHC) analysis or an IHC score of 2+ and negative results on in situ hybridization (ISH). Among the 557 patients who were randomly assigned 2:1 to trastuzumab deruxtecan or physician’s choice of single-agent chemotherapy, the median progression-free survival (PFS) was 9.9 months in the trastuzumab deruxtecan group vs 5.1 months in the physician’s choice group (HR, 0.50; 95% CI, 0.40-0.63; P < .0001). Overall survival (OS) was 23.4 months with trastuzumab deruxtecan vs 16.8 months with physician’s choice (HR, 0.64; 95% CI, 0.40-0.86; P = .003).³

In addition to extending PFS and OS, trastuzumab deruxtecan was also better tolerated than the chemotherapies that physicians selected. Adverse events of grade 3 or higher were observed in 52.6% of the patients who received trastuzumab deruxtecan and 67.4% of those who received physician’s choice. Adjudicated, drug-related interstitial lung disease or pneumonitis occurred in 12.1% of the patients who received trastuzumab deruxtecan, and 0.8% of patients died.

News of the results elicited a rare standing ovation at the ASCO meeting, and the FDA subsequently approved the agent for the treatment of patients with HER2-low metastatic disease in August 2022 (TABLE).²

DEFINING HER2-LOW DISEASE

Establishing definitive parameters for HER2-low disease is still a task set before oncologists and pathologists. Approximately 60% of breast cancers qualify as HER2 low based on the definition in DESTINY-Breast04.³ And although targeted drugs have transformed outcomes for the 15% to 20% of patients with breast cancer with significantly elevated HER2 expression, this was the first time that a drug targeted at HER2 proved beneficial to patients who met this definition of HER2-low breast cancer.⁴

HER2 is a membrane tyrosine kinase expressed at low levels by many healthy cells that is dramatically overexpressed (40- to 100-fold) by a minority of cancers that can have several million HER2 receptors per cell.²

“Existing IHC assays were optimized to distinguish overexpression from normal expression. They have an adequate dynamic range for that purpose but are suboptimal to distinguish different HER2 groups among tumors with lower levels of expression. Almost all breast cancers do express some HER2, and an IHC result of 0 is often the result of an artifact caused by formalin fixation rather than truly representing no HER2 protein present. For that reason, current IHC assays are unfit for the purpose of creating a new category of HER2 low,” said Antonio C. Wolff, MD, a professor of oncology at Johns Hopkins University and director of breast cancer trials in the Women’s Malignancies Program at Johns Hopkins Kimmel Comprehensive Cancer Center in Baltimore, Maryland. “Therefore, rather than creating a new category, for now it is better to simply describe the eligibility criteria used for the study to identify patients who could be candidates for this drug.”

Testing HER2 expression levels has long been a challenge. In 2007, nine years after the initial approval of trastuzumab (Herceptin), an expert panel convened by ASCO and the College of American Pathologists (CAP) concluded that both IHC and ISH returned inaccurate results in approximately 20% of cases. They recommended testing standards for HER2 overexpression that, among other improvements, sometimes combined the
2 methods to reduce the error rate. Those first ASCO/CAP guidelines were updated in 2013 and again in 2018, but even the most recent guidelines make no mention of HER2-low cancers. They also give no advice for separating cancers with small amounts of HER2 expression from cancers that do not express HER2 at all, as the authors note, “data from [the NSABP-B-47; NCT01275677 trial] confirmed the lack of benefit from adjuvant trastuzumab for patients whose tumors lack gene amplification and are IHC 1+ or 2+.” Consequently, HER2 gene amplification assessed by ISH or protein overexpression assessed by IHC remains the primary predictor of responsiveness to HER2-targeted therapies in breast cancer.7

Amplification or overexpression of HER2 has long been known to drive tumor growth and aggressiveness. Before the development of targeted therapies, HER2-positive status was associated with shorter survival.1 The question now, which has been investigated in a pair of recent studies, is whether having low levels of HER2 expression produce different cancer progression and outcomes than having no HER2 at all.

In the first of those studies, findings from which were presented at the 2022 ASCO meeting, investigators mined the National Cancer Database for outcome data on patients with metastatic breast cancer whose cancers scored 0 (HER2 0) or 1+2+/2+ (HER2 low) on IHC testing. There were no differences between the 6765 HER2-0 patients and the 17,771 HER2-low patients in age, race, year treated, location, income, insurance status, Charlson Deyo comorbidity index score, laterality, T stage, N stage, or use of systemic therapy. There was, however, a difference in hormone receptor status; HER2-low tumors were half as likely to have concomitant hormone receptor-negative status. Among hormone receptor-negative patients, the 3-year survival rate was 33.8% for HER2-low and 32.2% for HER2-0 patients. Among hormone receptor-positive patients, the survival rate was 60.9% in HER2-low and 55.6% in HER2-0 patients. HER2-low status was associated with longer survival on multivariable regression analysis (HR, 0.91; 95% CI, 0.87-0.95), even with propensity score matching (HR, 0.92; 95% CI, 0.89-0.96). In a subset analysis isolated to hormone receptor-positive cases, HER2 low remained correlated with improved survival (HR, 0.93; 95% CI, 0.89-0.98) with propensity-matched multivariable regression analysis.5

In the second study, whose results were published in JAMA Oncology, investigators compared outcomes of 5235 consecutive patients with nonmetastatic HER2-low or HER2-0 breast cancer who underwent surgery between January 2016 and March 2021 at Dana-Farber Brigham Cancer Center in Boston, Massachusetts. Although the patient populations were different (metastatic vs nonmetastatic cancers), the definitions of HER2 low (IHC score of 1+ or 2+) and HER2 0 (IHC score of 0) were the same as in the previously mentioned study. Also, in that study, hormone receptor expression was significantly more common among HER2-low tumors than HER2-0 tumors (90.6% vs 81.8%; P < .001). Investigators also found a correlation between the expression of estrogen receptors (ERs) and HER2. Patients with HER2-0 tumors experienced higher pathologic complete response rate (pCR) than patients with HER2-low tumors after neoadjuvant chemotherapy (26.8% vs 16.6%; P = .002). However,

### Expert Perspectives

**Hamilton Highlights the Changes to the Language of HER2**

*by BRITTANY LOVELY*

THE CONTINUUM OF HER2 expression in breast cancer has been an evolving topic in the field for several years, according to Erika P. Hamilton, MD. In a presentation during the 21st Annual International Congress on the Future of Breast Cancer® West, Hamilton said that multidisciplinary collaboration between pathologist and breast oncologists is key to staying informed of not only the classification actionable HER2 mutations but also the evolving definition of expression.

“What we traditionally classify as HER2 low is not HER2 0 and it is not what’s traditionally considered HER2 positive—IHC [immunohistochemistry] 3+. For patients [with HER2-low disease] they may have tumors that are 1+ or 2+ by IHC and ISH [in situ hybridization] negative,” said Hamilton, who is the director of the Breast and Gynecologic Cancer Research Program at Sarah Cannon Research Institute in Nashville, Tennessee.

Using this definition, the prevalence of HER2-low disease in patients with hormone receptor–positive breast cancer (n = 5563) was approximately 75%, with 27% of patients having HER2 IHC 1+ and 48% having IHC 2+ expression. For triple-negative breast cancer, Hamilton noted that HER2-low disease was less common but still reported among approximately half of patients (n = 607).1

Investigators have challenged the rationale that patients must have IHC 3+ to derive benefit from HER2-targeted agents for several years. For example, in the phase 3 NSABP-B-47 trial (NCT01275677) investigators evaluated the efficacy of adjuvant trastuzumab (Herceptin) and chemotherapy in patients with what was then defined as HER2-negative disease (IHC 1+ or 2+).2

Data from NSABP-B-47 did not show a clinical benefit in invasive disease-free survival with the addition of trastuzumab to chemotherapy for patients with an HR of 0.98. “You cannot tell what color line that was supposed to be [on the Kaplan-Meier curve] because they’re lying right on top of each other,” Hamilton said. She added that despite these early misses with first-generation tyrosine kinase inhibitors (TKIs), the difference now is the availability of new agents.

The most prominent agent is the antibody-drug conjugate (ADC) fam-trastuzumab deruxtecan-nxki (Enhertu). “[This is] a humanized, anti-HER2 monoclonal antibody, [with the] same amino acid sequences as trastuzumab, with a drug linker and an exatecan derivative payload. The drug to antibody ratio is 8:1 and it is a topoisomerase I inhibitor payload with a short systemic half-life. [It’s] also highly membrane permeable, which enables a bystander effect that we think may be particularly important and having such great activity even where HER2 [expression] may be low or heterogeneous,” Hamilton explained.

Early efficacy with the agent was demonstrated in a phase 1b (NCT02564900) trial of 54 patients with HER2-low metastatic breast cancer.3 Treatment with trastuzumab deruxtecan at 5.4 or 6.4 mg/kg elicited an objective response rate (ORR) of 37% (95% CI, 24.3%-51.3%) with a disease-control rate of 87% and a median duration of response (DOR) of 10.4 months (95% CI, 8.8-9.8 months).4 “What I think is even more impressive is the disease control rate approaching 90%, the DOR of at least 10 months, and progression-free survival [PFS] of almost a year,” Hamilton said.
Breast Cancer

**FIGURE. Examples of HER2 Expression via Immunohistochemistry Staining**

<table>
<thead>
<tr>
<th>Score</th>
<th>Pattern Description</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No observable staining, or membrane staining that is incomplete and is faint/barely perceptible in &lt; 10% of tumor cells</td>
<td>Negative</td>
</tr>
<tr>
<td>1+</td>
<td>Incomplete membrane staining that is faint/barely perceptible in &gt; 10% of invasive tumor cells</td>
<td>Negative</td>
</tr>
<tr>
<td>2+</td>
<td>Circumferential membrane staining that is incomplete and/or weak/moderate in &gt; 10% of invasive tumor cells, or complete and circumferential intense membrane staining in &lt; 10% of invasive tumor cells</td>
<td>Equivocal</td>
</tr>
<tr>
<td>3+</td>
<td>Homogeneous, dark, circumferential pattern in &gt; 10% of invasive tumor cells</td>
<td>Positive</td>
</tr>
</tbody>
</table>


Experts Perspectives

noted. The median PFS was 11.1 months (95% CI, 7.5-NE). To decipher the mechanism of action that allows for trastuzumab deruxtecan to elicit a benefit in this subgroup of patients, investigators examined the bystander effect of the ADC. The classic ADC mode of action involves the agent binding to a HER2 receptor and being internalized into the cell by endocytosis, which is when the payload is released and has a cytotoxic effect.

The bystander killing effect, on the other hand, involves the release of the drug payload from the antibody after antigen binding prior to internalization. This results in the drug payload in the intracellular space due to a high drug membrane permeability and, as you can imagine, if you have HER2 expression on some cells, and maybe not as much on cells around them, this is a way to target all of those cells,” Hamilton explained.

Building on the results observed in the phase 1b trial, investigators leveraged the bystander killing effect in the phase 3 DESTINY-Breast04 trial (NCT03734029). An exploratory analysis was conducted for patients with hormone receptor–negative disease as there were only 60 patients that met the criteria, Hamilton continued. “[Despite the] very small numbers it looks no worse with a PFS of 2.9 months with physician’s therapy of choice increasing to 8.5 months with trastuzumab deruxtecan. The PFS for more aggressive triple-negative patients in general is shorter, but the spread is still the same with an increased magnitude of benefit for trastuzumab deruxtecan,” said. The HR for PFS was 0.46. Hamilton noted that OS data for these patients are also encouraging, at 18.2 months with trastuzumab deruxtecan vs 8.3 months with TPC (HR, 0.48). “These results really will establish trastuzumab deruxtecan as a new standard of care for HER2-low metastatic breast cancer and that really encompasses both hormone receptor–positive [disease] as well as patients we would typically consider triple-negative,” Hamilton said. She added that the safety data in the trial demonstrated no new toxicity signals.

“[This results in] the drug payload in the intracellular space due to a high drug membrane permeability and, as you can imagine, if you have HER2 expression on some cells, and maybe not as much on cells around them, this is a way to target all of those cells,” Hamilton explained.

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very critical to understand if tumors are HER2-low positive, not because it’s associated with a different prognosis, but rather because it’s allowing you to utilize a very novel therapy that can dramatically impact patient’s outcomes.”

Of course, given that both studies used IHC to separate patients whose tumors were HER2 low from those whose tumors were HER2 0, some tumors were categorized incorrectly in both studies. Indeed, in data from a new study from Yale Cancer Center in New Haven, Connecticut, investigators concluded that current IHC tests struggle severely to differentiate between IHC 1+ and IHC 0 tumors.

In this study, investigators collected data from a survey conducted by CAP and a Yale-based study of concordance among 18 pathologists reading 170 breast cancer biopsies. The CAP analysis showed that 19% of the cases read by 1400 laboratories generated results with less than 70% agreement between a HER2 score of 0 vs 1+. In the second part of the study, in which 18 pathologists read the same slides from a selected set of breast cancer biopsies using the 4-point scale, there was only 26% agreement among pathologists on scores of 0 and 1+.

Investigators said the disagreement was due to the poor quality of the current IHC test in this critical range that will likely determine which women are eligible for trastuzumab deruxtecan.11

“Although the test returns 4 different scores—0, 1, 2, or 3—it is not actually designed to differentiate 0s from 1s. It’s designed to give you a yes/no answer about whether a tumor massively overexpresses HER2 in a way that would make trastuzumab a good treatment,” said senior study author David Rimm, MD, PhD. Rimm is the Anthony N. Brady Professor of Pathology and a professor of medicine at Yale University School of Medicine. He also serves as director of Yale Pathology Tissue Services, director of the Yale Cancer Center Tissue Microarray Facility, and director of the Physician Scientist Training Program in Pathology Research. “We’ve always known this, but the results of this study indicate that the biggest factor in determining whether a result is interpreted as a 0 or a 1+ is chance, and that will likely lead to the mismanagement of many patients in terms of who gets treated with trastuzumab deruxtecan.”

Is it possible to develop a test that more accurately distinguishes tumors with low HER2 expression from those with no HER2 expression (FIGURE12)? “We’ve already developed one,” Rimm said, adding that diagnostic companies are also developing higher sensitivity tests because of the large unmet need. “Of course, you’d need to validate any test that’s developed, but that can be done in a reasonable time frame.”

The IHC test’s inability to differentiate between low and nonexistent levels of HER2 expression also creates a potential problem with the DESTINY-Breast04 results. “To be eligible for the study, patients needed to have a tumor that tested HER2 IHC 1+ or IHC 2+ without gene amplification. Patients with IHC 0 were not eligible for the study, and it is quite plausible that this antibody-drug conjugate would be active in them too, but this must be confirmed,”

we’re probably going to see even more patients that have at least an IHC 1+.”

Hamilton said that the medical oncologist also has a role in changing the way HER2 status is communicated. “We must make sure that we change the wording in our notes now that this is actionable. Even my notes up until several years ago, when we started having [trastuzumab deruxtecan] in the clinic, would say HER2 negative by ISH. That no longer tells the whole story. We need to make sure that we start capturing who are our patients who have IHC 1+ or 2+ and are HER2 low.” Diving even further into HER2-low disease, Hamilton noted that the DAISY trial (NCT01413960) is evaluating trastuzumab deruxtecan in patients with HER2-low and HER2-null (IHC 0+) metastatic breast cancer.2 With the benefit seen here, Hamilton said that a shift in HER2 with an IHC of 0+ may no longer be appropriate terminology as it may be separate from HER2-negative disease. “Another way to say this is HER2-null, and I would encourage us all to maybe start talking about HER2 with a little bit different terminology: HER2 positive or amplified, HER2 low, and then HER2 0 or null. I don’t think we’re going to know what HER2 negative really means anymore.”

Expanding on that, Hamilton said IHC 0 is has imperfect connotations. “If we talk to our pathology colleagues, HER2 IHC 0 does not mean there’s not any HER2; you can actually have thousands of copies of HER2 on the cell and still be classified as a 0,” she said, noting that challenging these standards will rely on more results among patients with IHC 0 disease.

Although trastuzumab deruxtecan may be at the forefront of these conversations, other agents are making their mark in the HER2 landscape. These include trastuzumab duocarmazine (SYD985) and zenocutuzumab, a novel HER2/HER3 bispecific antibody.

“What do we have coming in ongoing and planned trials enrolling [patients with] HER2-low disease? [Well,] a slew of ADCs and [ado-trastuzumab emtansine (Kadcyla)] and trastuzumab deruxtecan are not going to be the only ones at the party any longer: We also have novel HER2 TKIs as well as HER2 vaccines,” Hamilton said.

**Identifying Actionable Targets in HER2-Mutant Disease**

Hamilton pointed out that among patients with HER2-mutant disease, identifying and sorting targets that will respond to therapy requires a nuanced approach. “There are at least 36 unique HER2-activating mutations that have been identified and counting,” she said. “What makes it tricky for us, as oncologists in the clinic, is not all HER2 mutations are actionable, and trying to figure out which ones are and which ones are not activating and therefore not actionable for our patient can be a little bit difficult.”
Wolff said. Some evidence exists about the effect of trastuzumab deruxtecan in patients whose tumors receive IHC scores of 0 from the phase 2 DAISY trial (NCT04132960), which reported results during the European Society for Medical Oncology Breast Cancer Congress 2022 and the 2021 San Antonio Breast Cancer Symposium.

Investigators in DAISY assigned 186 patients with metastatic breast cancer to 1 of 3 cohorts based on HER2 IHC expression: IHC 3+ or IHC 2+/ISH+ (cohort 1; n = 68); IHC 2+/ISH- or IHC 1+ (cohort 2; n = 72); and IHC 0+ (cohort 3; n = 37). All patients received 5.4 mg/kg trastuzumab deruxtecan intravenously on day 1 of 21-day cycles.

Best objective response (BOR) favored cohort 1 (71.0%; 95% CI, 58.3%-81.0%) over cohort 2 (37.5%; 95% CI, 26.4%-50.0%) and cohort 3 (30.0%; 95% CI, 16.0%-47.0%). Investigators also found that those in cohort 1 had the longest median PFS at 11.1 months compared with 6.7 months in cohort 2 and 4.2 months in cohort 3.1,13 These results indicate that trastuzumab deruxtecan is more effective in patients with IHC scores of 1+ than it is in patients with IHC scores of 0, but it says nothing about the relative effectiveness of trastuzumab deruxtecan vs other treatments in patients with IHC scores of 0. It is therefore possible that many such patients would receive some benefit.

“I predict that a lot of savvy oncologists will, upon having a patient’s IHC test come back 0, advise that patient to send the sample to be read at a different lab, knowing there’s a strong chance it will be upgraded to a 1 and they will qualify for this treatment,” Rimm said. “Patients will want to try this medication. Those results were spectacular.”

REFERENCES

Expert Perspectives

Hamilton noted that when discussing HER2 it is important to separate HER2 mutations from HER2 overexpression or amplification. “Amplification is where we talk about too much of a receptor driven by the HER2 mutation and it can either be activating or it cannot be activating,” she said. Amplifications can occur in several locations including the transmembrane or extracellular kinase domain, and overexpression is present in approximately 15% to 20% of breast cancers. HER2 mutations, on the other hand, are rarer and are present in approximately 3% to 4% of HER2-nonamplified cancers.1

“Most of the mutations that we’re aware of occur in the kinase domain,” Hamilton said, adding that this accounts for 70% of the mutations that are mostly in exons 19 and 20. An additional 20% of mutations are found in the extracellular domain. In terms of targetability, Hamilton noted that of the known HER2-activating mutations, some are insensitive to or resistant to first- and second-generation TKIs, but that newer agents have been shown to be effective.

Hamilton shared data from a personalized medicine team at Sarah Cannon showing that the frequency rate of HER2-activating mutations among 306 patients with HER2-mutant breast cancer was 48%. Across 2161 patients with HER2-mutant solid tumors the frequency rate was 30%. Although the rates were higher in the breast cancer cohort, Hamilton noted that only half of patients had targetable markers and sensitivity to anti-HER2 therapies varied across agents.1

“What are our options for cancers that have HER2 mutation?” Hamilton asked. “What makes it tricky is that the [mutations] do not all [respond] the same to different TKIs. Mutations are not all created the same; some are sensitive to one TKI and may be resistant to another. This certainly becomes complex when you have an individual patient [in whom] you see HER2 mutation. First, you [must] think if HER2 mutation is actionable, and then what TKI may be most appropriate.”

Several studies are underway to establish a better understanding of the mutations that have greater sensitivity to available and investigational therapies.1
1L aRCC treatment that OFFERS A BALANCE OF DATA:
superior OS,* safety & tolerability, patient-reported quality of life†‡

*vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; P=0.001); median OS was not reached in either arm.1,4

† The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.4
‡ Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.4,6

INDICATIONS
CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hagemnosis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.
Superior outcomes: results in the ITT population\(^{1,3,4}\)
(median follow-up time of 18.1 months; range: 10.6-30.6 months)

<table>
<thead>
<tr>
<th>MEDIAN PFS WAS DOUBLED*</th>
<th>ORR WAS DOUBLED*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>16.6 months</strong></td>
<td><strong>55.7%</strong></td>
</tr>
<tr>
<td>CABOMETYX + OPDIVO</td>
<td>CABOMETYX + OPDIVO</td>
</tr>
<tr>
<td>(95% CI: 12.5-24.9; n=323)</td>
<td>(95% CI: 50.1-61.2; n=323)</td>
</tr>
<tr>
<td>vs 8.3 months sunitinib</td>
<td>vs 27.1% sunitinib</td>
</tr>
<tr>
<td>(95% CI: 0.41-0.64; (P&lt;0.0001))</td>
<td>(95% CI: 22.4-32.3; n=328)</td>
</tr>
</tbody>
</table>

\(*PFS and ORR were assessed by BICR.\)

**CheckMate-9ER study design**

A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.\(^{1,3,4}\)

**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS**

**Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

**Diarrhea:** Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

**Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Hepatotoxicity:** CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (\(n=9\)) or nivolumab (\(n=11\)) as a single agent or with both (\(n=24\)), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

**Adrenal Insufficiency:** CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC. Approximately 80% (32/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (\(n=4\)) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (\(n=6\)) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

**Thyroid Dysfunction:** Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

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**DISCOVER THE BALANCE OF DATA AT CABOMETYXhcp.com**

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\(\text{© 2021 Exelixis, Inc.} \quad \text{CA-1749-2} \quad \text{09/21} \quad \text{OPDIVO® and the related logo is a registered trademark of Bristol-Myers Squibb Company.} \)
Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

**Hypocalcemia:** CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients. Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume a reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

**Embryo-Fetal Toxicity:** CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

**ADVERSE REACTIONS**
The most common (≥20%) adverse reactions are:

- CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.
- CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

**DRUG INTERACTIONS**

- **Strong CYP3A4 Inhibitors:** If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.
- **Strong CYP3A4 Inducers:** If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John’s wort.

**USE IN SPECIFIC POPULATIONS**

- **Lactation:** Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

**Hepatic Impairment:** In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

**References:**

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.
CABOMETYX® (cabozantinib) TABLETS
BRIEF SUMMARY OF PRESCRIBING INFORMATION.
PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE
1.1 Renal Cell Carcinoma
CABOMETYX® is indicated for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX® in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX® is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differeniated Thyroid Cancer
CABOMETYX® is indicated for the treatment of adult and pediatric patients 12 years of age or older with locally recurrent or metastatic, differentiated thyroid cancer (DTC) that has progressed following prior VEGF-targeted therapy and who are radioactive iodine-refractory or ineligible.

2 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 9% in CABOMETYX patients in the RCC, HCC, and DTC studies.

5.2 Perforations and Fistulas
Fistulas, including fatal fistulas, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in ≥ 5% (including pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (Grade 1), 17% (Grade 2), and 1% (Grade 4) of CABOMETYX-treated patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX and interrupt CABOMETYX treatment to Grade 1 and resume CABOMETYX at a reduced dose for irritable bowel 2% or Grade 3 PPI.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-planter erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drug is administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and/or reduce dose for intolerable Grade 2 PPE or Grade 3 PPE.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-Plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinaemia, Osteonecrosis of the Jaw, Impaired Wound Healing, Respiratory, Thoracic, and Mediastinal Events, Skin and Subcutaneous Tissue.
daily 4 weeks on treatment followed by 2 weeks off, until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 37.3) for patients receiving CABOMETYX and 3.8 months (range 0.2 – 37.3) for patients receiving sunitinib. The most frequent Grade 3-4 adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients were hypertension, diarrhea, rash, hypothyroidism, and musculoskeletal pain. Adverse reactions leading to discontinuation of cabozantinib or sunitinib occurred in 23% of patients: 41% CABOMETYX only, 5% sunitinib only, and 5% both drugs due to the same adverse reaction at the same time. All Grade 3-4 adverse reactions occurring in ≥ 25% of patients treated with CABOMETYX were diarrhea, rash, fatigue, hypothyroidism, PPE, fat embolism, skin embolism, and hypoglycemia. The most common adverse reactions reported in ≥ 25% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hypothyroidism, PPE, rash, musculoskeletal pain, decreased appetite, nausea, dyspepsia, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥15% of Patients receiving CABOMETYX and Nivolumab-CHEKEMATE-I/ER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX and Nivolumab (n=361)</th>
<th>Sunitinib (n=320)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Diarrhea</td>
<td>64</td>
<td>7</td>
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<tr>
<td>Nausea</td>
<td>27</td>
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<tr>
<td>Peripheral edema</td>
<td>32</td>
<td>1.1</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>22</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1.9</td>
</tr>
<tr>
<td>Dyspepsia*</td>
<td>15</td>
<td>1.4</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
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<td></td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal or abdominal pain</td>
<td>20</td>
<td>0.3</td>
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<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
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<td></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal inflammation</td>
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<td>2</td>
</tr>
</tbody>
</table>

Table 5. Laboratory Values Worsening from Baseline for Patients receiving CABOMETYX and Nivolumab-CHEKEMATE-I/ER

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX and Nivolumab</th>
<th>Sunitinib</th>
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<tr>
<td>Increased alkaline phosphatase</td>
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<td>2.8</td>
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Table 6. Adverse Reactions Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=487)</th>
<th>Placebo (n=237)</th>
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</table>
In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age. In COSMIC-311, 50% of 121 patients treated with CABOMETYX were age 65 years or older and 12% were ≥75 years of age.
New JAK Inhibitors and Emerging Novel Agents Expand Myelofibrosis Treatment Arsenal

by CHRISTINA T. LOGUIDICE

FOR PATIENTS WITH MYELOFIBROSIS (MF), stem cell transplant continues to be the only curative treatment. Many patients, however, may not be eligible for transplants, including older adults or those whose disease is not yet deemed of high enough risk to warrant transplant. In these patients, medical treatments are crucial to control their symptoms and improve their overall quality of life.

In terms of myeloproliferative neoplasms, MF “is probably the most symptomatic disease, with a high burden on patients and worse outcome in general,” Rami Komrokji, MD, said during a recent OncLive Peer Exchange®. Komrokji served as moderator for a panel of hematology cancer experts who discussed the current treatment landscape and novel emerging therapies for patients with MF.

JAK INHIBITORS

Three JAK inhibitors have been approved for patients with MF: ruxolitinib (Jakafi), fedratinib (Inrebic), and pacritinib (Vonjo). Momelotinib is on track to become the fourth FDA-approved JAK inhibitor.

Ruxolitinib

Ruxolitinib has been the standard of care for many patients with MF since 2011, when it became the first FDA-approved treatment for patients with MF. The initial approval was for patients with intermediate/high-risk primary or secondary MF based on data from the COMFORT-I (NCT00952289) and COMFORT-II (NCT00934544) trials. Both studies showed statistically significant reductions in spleen volume and improvement in total symptom scores (TSSs). “It was transformative because we had a treatment that improved patients’ quality of life and reduced spleen size,” Jamile Shammo, MD, said.

During the 2022 American Society of Clinical Oncology Annual Meeting (2022 ASCO) in June, a retrospective review of the medical records of 131 patients who received ruxolitinib for 3 or more years was presented. The study found that 40% of patients who remained on ruxolitinib for 3 or more years were alive 10 years after their treatment initiation. On multivariate analysis, age 65 years or older and neutropenia were predictive factors of survival.

“IT’s a very good option for patients who have this disorder. We need to keep an eye on things like opportunistic infections—herpes zoster is 1 such issue—and cytopenias, which can be managed,” Shammo said.

Fedratinib

Fedratinib became the second FDA-approved JAK inhibitor for patients with intermediate-2

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“CURRENT AND FUTURE TRENDS IN MYELOPROLIFERATIVE NEOPLASMS”

MODERATOR

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To watch the entire OncLive Peer Exchange® discussion, scan the QR code or visit bit.ly/3cuyPMA
or high-risk primary or secondary MF when it was finally approved in 2019 based on data from the JAKARTA (NCT01437787) and JAKARTA-2 (NCT01523171) studies. Its development had been slowed because it was placed on a clinical hold between 2013 and 2017.

“Approval of the drug was delayed because there was a very low rate of Wernicke encephalopathy [WE], probably interfering with thiamine metabolism to a small degree,” Ruben Mesa, MD, explained. WE had been observed in 1.3% of patients (8 of 608 study participants).

“There’s a black box warning that sounds scary but in practice is fairly simple. You check thiamine levels, and you replace thiamine, and thiamine is dirt cheap. I give patients a bottle. Then you monitor for Wernicke,” Mesa said.

Once it was determined that fedratinib does not directly induce WE and that the risk of the complication can be mitigated, the FDA approved it. Data from the JAKARTA studies showed statistically significant responses in spleen volume reduction (SVR) and MF symptoms. “If [patients] used ruxolitinib and still have [an enlarged] spleen and symptoms, and you don’t have a trial available, fedratinib is a good option. It can be used at full dose in patients with platelets between 50,000 and 100,000 per mm³,” Mesa said.

**Pacritinib**

Pacritinib received an accelerated approval from the FDA in February 2022 for adult patients with intermediate or high-risk primary or secondary MF based on data from the pivotal phase 3 PERSIST-2 (NCT02055781) study.1,3 PERSIST-2 randomly assigned 311 patients 1:1:1 to receive pacritinib 200 mg twice daily (n = 107), pacritinib 400 mg once daily (n = 104 patients), or best available therapy (BAT; n = 100), usually ruxolitinib (45% of patients). Prior JAK2 inhibitor therapy was permitted.

At week 24, the intention-to-treat efficacy population included 72 to 75 patients in each arm, and significantly more patients in the pacritinib arms vs BAT arm had SVR of 35% or greater (18% vs 3%, respectively; P = .001). Additionally, pacritinib—vs BAT-treated patients had a nonsignificantly higher rate of reduction in TSS of 50% or greater (25% vs 14%, respectively; P = .08).

When comparing pacritinib dosing, pacritinib 200 mg twice daily was found to be the most efficacious, demonstrating significant reductions in both spleen volume and TSS vs BAT, with 22% vs 3% (P = .001), respectively, experiencing SVR, and 32% vs 14% (P = .01), respectively, experiencing reduction in TSS of 50% or greater.

Unlike ruxolitinib and fedratinib, pacritinib can be used irrespective of patients’ platelet counts and in the setting of marked thrombocytopenia. Mesa explained that this has been attributed to its inhibition of IRAK1. “It might be better for patients with cytopenic MF. In clinical studies, it could be used safely and effectively in individuals with platelet counts of less than 50,000 per mm³. It’s approved for individuals with marked thrombocytopenia in the front line and second line. It might also help to improve anemia,” he said, noting it is the first approved therapy that addresses the needs of patients with cytopenic MF, a group who previously had no treatment options.

**Momelotinib**

Momelotinib, a highly selective JAK inhibitor, is being developed for patients with MF who are symptomatic and anemic. GSK has submitted a new drug application for momelotinib based on data from several studies, including the phase 3, randomized, double-blind MOMENTUM (NCT04173494) trial. The FDA is scheduled to make a decision by June 16, 2023.

“[Momelotinib is] a JAK1 and JAK2 inhibitor that we had noticed early on could help improve anemia. Just as we had learned early on that pacritinib may have less thrombocytopenia, momelotinib had something different. It might help to improve anemia and have less drug-emergent anemia,” Mesa said.

Momelotinib was first assessed in the phase 3 SIMPLIFY-1 (NCT01969838) and SIMPLIFY-2 (NCT02101268) trials.7,8 In SIMPLIFY-1, 432 patients with either high-risk, intermediate-2 risk, or symptomatic intermediate-1 risk MF who had not received JAK inhibitor therapy were randomly assigned 2:1 to receive momelotinib 200 mg once daily or ruxolitinib 20 mg twice daily, after which all patients could receive open-label momelotinib. In SIMPLIFY-2, momelotinib was found to be noninferior to ruxolitinib for spleen response and inferior for symptom response, but momelotinib was associated with a reduced transfusion requirement.

“If we look at that analysis now, not inferior [for symptom response] probably would have been more accurate. But without question, it was better for anemia,” Mesa said. He explained that a multicenter analysis he participated in investigated the mechanism behind the improvement in anemia and discovered it was due to momelotinib’s suppression of hepcidin and inhibition of ACVR1.

SIMPLIFY-2 compared momelotinib with BAT in 156 patients with MF previously treated with ruxolitinib. At 24 weeks of treatment, 73 of 104 patients (70%) in the momelotinib arm and 40 of 52 patients (77%) in the BAT arm (ruxolitinib in 89% of patients) were still on treatment. Momelotinib was not superior to BAT in demonstrating a greater than 35% reduction in spleen size compared with baseline, with 7% vs 6% of patients, respectively, achieving this end point.

Because the data from SIMPLIFY-1 and SIMPLIFY-2 were muddy, the MOMENTUM trial was initiated to provide clarity. “We created the MOMENTUM study to have a very specific additional set of data that we thought were critical: second-line, symptomatic, and anemic patients who [did not have success with] ruxolitinib, and with a control arm that we think was arguably demonstrating that we don’t have a lot as it relates to anemia. But we do have danazol, an androgen,” Mesa said.

Data for the MOMENTUM trial were presented at 2022 ASCO (TABLE).9 The trial compared momelotinib with danazol in 195 patients with MF previously treated with a JAK inhibitor who were symptomatic and anemic. Patients were randomly assigned 2:1 to receive momelotinib 200 mg once daily plus danazol placebo (n = 130) or danazol 600 mg once daily plus momelotinib placebo (n = 65) for 24 weeks, after which patients could receive open-label momelotinib. At 24 weeks, 72.3% of patients in the momelotinib arm and 58.5% of patients in the danazol arm completed treatment, with 70.8% and 55.4% of these patients, respectively, entering the momelotinib open-label extension.

Momelotinib was found to be superior to danazol in almost all end points assessed, including TSS response rate (24.6% vs 9.2%, respectively; P = .0095), SVR of at least 25%
Momelotinib showed noninferiority to danazol in transfusion independence rate at 24 weeks (30.8% vs 23.1%, respectively; \( P = .0064 \)) and of at least 35% (23.1% vs 3.1%, respectively; \( P = .0006 \)). There was a trend toward improved overall survival (OS) with momelotinib-treated patients and 23% of danazol-treated patients. As in the overall intention-to-treat population, platelet levels in thrombocytopenic patients were found to remain stable over time, and the trend toward improved OS was maintained.

"When we look at the experience of momelotin in aggregate, it clearly paints a picture of a drug that would be very helpful to have in MF… It will have roles in some patients in the front line and clearly some patients in the second line. It will make a significant addition to the armamentarium if the drug is approved after all these data are reviewed by the FDA," Mesa said.

EMERGING TREATMENTS

In addition to JAK inhibitors, a variety of other novel agents with unique mechanisms of action are being tested in clinical trials as potential treatments for MF. The panelists indicated that some of these agents may lend themselves to promising combination approaches, particularly in combination with ruxolitinib, as well as provide patients with options after JAK2 inhibitor failure.

Navitoclax (ABT-263)

Navitoclax, a cousin of venetoclax (Venclexta), is an orally bioavailable small-molecule inhibitor of BCL2.\(^1\) Targeting the BCL-X pathway has been shown to overcome JAK inhibitor resistance in preclinical models.\(^1\) "For many reasons, it’s been speculated that the combination of trying to overcome apoptotic resistance and having JAK inhibition could be beneficial," Mesa said.

Recently, data from the phase 2 REFINE trial (NCT03222609) were reported. The study assessed the addition of navitoclax to ruxolitinib for patients with MF and progression or suboptimal response while on a stable dose of ruxolitinib (≥ 10 mg twice daily).\(^1\) At week 24, the addition of navitoclax to ruxolitinib was found to result in durable SVR of 35% or greater and improvements in TSS, hemoglobin response, and change in bone marrow fibrosis grade. Two phase 3 trials exploring the potential of the combination of navitoclax and ruxolitinib to modify the course of the disease are underway: TRANSFORM-1 (NCT04472598) in patients who have not received JAK2 inhibitors and TRANSFORM-2 (NCT04468984) in patients whose disease has progressed or who have had a suboptimal response to ruxolitinib therapy. The comparison arms in the trials are ruxolitinib plus placebo and BAT, respectively.\(^1\)

Pelabresib (CPI-0610)

Pelabresib is an investigational small molecule BET inhibitor that was assessed in the phase 1/2 MANIFEST trial (NCT02158858).\(^1\) In the study, pelabresib monotherapy showed signs of clinical activity in patients with advanced MF who were ineligible for JAK inhibitor therapy, including SVR, symptom improvement, and hemoglobin benefit.\(^1\)

Pelabresib is currently being assessed in the ongoing, global, phase 3, double-blind, randomized, placebo-controlled phase 3 MANIFEST-2 (NCT04603495) trial.\(^1\) MANIFEST-2 investigators are planning to enroll up to 400 patients with intermediate-1 or higher primary or secondary MF who have not been treated with a JAK inhibitor. Patients will be treated with ruxolitinib twice daily on days 1 to 21 in 21-day cycles and randomly assigned 1:1 to receive concomitant pelabresib or concomitant placebo orally once daily on days 1 to 14 of treatment. The primary end point will be SVR of 35% or greater at 24 weeks, and the secondary end point will be reduction in TSS of 50% or greater from baseline at 24 weeks.

"BET inhibition does provide a novel mechanism of treating MF, which will hopefully help and boost not only the effectiveness of ruxolitinib, the duration of time that it’s working, but also perhaps have some type of effect on the natural history of the disease," Jeanne M. Palmer, MD, said.

Imetelstat (GRN163L)

Imetelstat, a telomerase inhibitor, was evaluated in the phase 2, multicenter MYF2001 (NCT02426086) trial, which assessed 2 doses of imetelstat monotherapy in patients with relapsed or refractory intermediate-2 or high-risk MF previously treated with a JAK inhibitor.\(^1\) Patients were randomly assigned to receive either imetelstat 9.4 mg/kg or 4.7 mg/kg intravenously once...
In Tampa, Florida.15 were collected from a study of 96 patients who responded to JAK inhibitor treatment.16 intermediate-2 or high-risk MF who have not responded to JAK inhibitor treatment. Based on this OS signal, imetelstat is currently being assessed in relapsed or refractory myelofibrosis patients previously treated with a JAK inhibitor in a phase 3 randomized study of momelotinib versus danazol [MOMENTUM]. J Clin Oncol. 2022;40(suppl 16):7002. doi:10.1200/JCO.2022.40.16_suppl.7002

In the groups that have ruxolitinib failure, many studies have shown a survival in the range of a year and a half or less,” Komrokji said, indicating that the almost 30 months seen with imetelstat suggests an OS benefit.

The real-world comparison showed BAT to have a 12-month OS in closely matched patients with MF after JAK inhibitor failure. Based on this OS signal, imetelstat is currently being assessed in the phase 3 MYF3001 trial (NCT04576156) comparing imetelstat with BAT in patients with intermediate-2 or high-risk MF who have not responded to JAK inhibitor treatment.16

REFERENCES

Rami Komrokji, MD, discusses data on the recently approved agents fedratinib and pacritinib for myelofibrosis treatment.

Jamile Shammo, MD, explains the efficacy and safety of the 3 approved therapies for myelofibrosis.

Ruben Mesa, MD, discusses data he presented at ASCO 2022 on the novel agent momelotinib as Jeanne M. Palmer, MD, listens.
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

**Select Safety Information**

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

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CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.
RAISING THE STANDARD FOR SURVIVAL

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*1

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Important Safety Information

**Warnings and Precautions**

- **Diarrhea**: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity**: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity**: TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.
In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

**PRIMARY ENDPOINT**

**PFS**

46% reduction in the risk of disease progression or death

- HR = 0.54 (95% CI: 0.42–0.71); P < 0.00001
- Median PFS: 7.8 months (95% CI: 7.5–9.6) in the TUKYSA arm vs 5.6 months (95% CI: 4.2–7.1) in the control arm

**EXPLORATORY ANALYSIS**

**PFS AT 12 MONTHS**

~3x as many patients were progression-free

<table>
<thead>
<tr>
<th>TUKYSA ARM</th>
<th>CONTROL ARM</th>
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<tbody>
<tr>
<td>33% (33.1%; 95% CI: 26.6–39.7)</td>
<td>12% (12.3%; 95% CI: 6.0–20.9)</td>
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</table>

*Study design: HER2CLIMB was a randomized (2:1), double-blind, placebo-controlled trial of 612 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm: n = 410) or placebo + trastuzumab + capecitabine (control arm: n = 202). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause) PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.

†This exploratory analysis is descriptive only. These are estimates and not exact numbers. HER2CLIMB was not powered to assess a statistical difference between treatment groups at this time point.

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST. The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child–Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

**References:**

TUKYSA® (tucatinib) tablets, for oral use

Brief summary of Prescribing Information (PI). See full PI. Rx Only

INDICATIONS AND USAGE
TUKYSA® is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced, unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-targeted regimens in the metastatic setting.

DOSEAGE AND ADMINISTRATION

Recommended Dosage
The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablets if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time.

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions
The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea1</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Hepatotoxicity1,2

| Grade 2 bilirubin (>1.5 to 3 × ULN) | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level. |
| Grade 3 ALT or AST (> 5 to 20 × ULN) | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level. |
| Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN) | Permanently discontinue TUKYSA. |
| ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN | Permanently discontinue TUKYSA. |
| Other adverse reactions3 | |
| Grade 3 | Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level. |
| Grade 4 | Permanently discontinue TUKYSA. |

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

Adverse Reaction | TUKYSA + Trastuzumab + Capecitabine (N = 404) | Placebo + Trastuzumab + Capecitabine (N = 189) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea1</td>
<td>32 (12.6%)</td>
<td>21 (11.1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>58 (19.2%)</td>
<td>44 (23.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36 (12.8%)</td>
<td>25 (13.2%)</td>
</tr>
<tr>
<td>Rash1</td>
<td>32 (12.4%)</td>
<td>21 (11.3%)</td>
</tr>
</tbody>
</table>
| Gastrointestinal disorders
| Diarrhea        | 81 (23.2%)                                     | 53 (28.0%)                                    |
| Nausea          | 58 (17.1%)                                     | 44 (23.6%)                                    |
| Vomiting        | 36 (11.0%)                                     | 25 (13.5%)                                    |
| Rash1           | 32 (10.0%)                                     | 21 (11.6%)                                    |

Skin and subcutaneous tissue disorders

| Palmar-plantar erythrodysesthesia syndrome | 63 (19.0%) | 53 (27.9%) |
| Rash1                                      | 20 (6.5%)  | 15 (8.1%)  |

Hepatobiliary disorders

| Hepatotoxicity | 42 (13.3%) | 9 (4.8%)  |
| Metabolism and nutrition disorders
| Decreased appetite | 20 (6.5%) | 0 (0.0%) |

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the full Prescribing Information for trastuzumab and capecitabine for pregnancy and contraception information.

ADVERSE REACTIONS

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.

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA included diarrhea (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)
CYP3A Substrates: Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors. CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

**DRUG INTERACTIONS**

**Effects of Other Drugs on TUKYSA**

**Strong CYP3A Inducers or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inhibitor decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inhibitor.

**Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

**Effects of TUKYSA on Other Drugs**

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates.

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**Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB**

<table>
<thead>
<tr>
<th></th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥3</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>47</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>Increased AST</td>
<td>43</td>
<td>6</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>40</td>
<td>0.8</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>26</td>
<td>2.5</td>
</tr>
<tr>
<td>Increased alkaline phosphate</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NC-CTCAE v4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NC-CTCAE v5.0).
   2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
   3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
   4. There is no definition for Grade 2 in CTCAE v4.03.
   5. Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increased persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

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**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk.

In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

**Lactation**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

**Females and Males of Reproductive Potential**

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

**Contraception:**

- Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.
- Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

**Infertility:**

Based on findings from animal studies, TUKYSA may impair male and female fertility.

**Pediatric Use:**

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

**Geriatric Use:**

In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

**Renal Impairment:**

The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capcitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [Ccr] ≥ 30 to 89 mL/min).

**Hepatic Impairment:**

Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

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**Seagen**

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CEACAM5 Shows Great Potential as Therapeutic Target in NSCLC

by KYLE DOHERTY

RESEARCH EXAMINING novel treatment options for patients with non–small cell lung cancer (NSCLC) actionable mutations has drastically expanded the treatment landscape for smaller subsets of patients. Soon that may include those with carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5)-expressing tumors. The target has recently displayed great potential for investigators as a therapeutic target.

CEACAM5 is a cell surface glycoprotein that is not highly expressed in several normal tissues, including colon, esophagus, and head and neck. However, the protein is often highly expressed in a few tumor types, such as gastrointestinal, breast, and lung. Approximately 20% of patients with NSCLC exhibit overexpression of CEACAM5.1,2

“CEACAM5 is expressed primarily on adenocarcinomas but does have some expression in squamous tumors, as well,” Paul Bunn, MD, the James Dudley Chair in Cancer Research and a distinguished professor of medicine–medical oncology at the University of Colorado Anschutz Medical Campus in Aurora, said during an OncLive® scientific interchange and workshop. “This antigen is associated with tumor progression. It promotes cell proliferation and migration. It is expressed much more in lung tumors than in normal lung [tissue]. Therefore, it is amenable to development of antibody-drug conjugates [ADCs].”

Investigators have reported that high CEACAM5 expression may be associated with cell proliferation and migration.1 CEACAM5 can be detected using immunohistochemical (IHC) assays. Positive staining has been defined as any partial or complete tumor cell plasma membrane staining at a minimum of 2+ intensity.2 The definition is being used for patient selection and stratification in ongoing phase 2 and phase 3 clinical trials of the potential first-in-class CEACAM5-targeted agent tusamitamab ravtansine (formerly SAR408701).

NOVEL CEACAM5-TARGETED AGENT DISPLAYS PROMISING EARLY RESULTS IN NSCLC

Tusamitamab ravtansine is an ADC consisting of a humanized monoclonal antibody and a cytotoxic maytansinoid, DM4. The monoclonal antibody binds to CEACAM5 and the maytansinoid targets CEACAM5-expressing tumor cells. In preclinical studies, the agent was proven to selectively bind to CEACAM5 in human tissue and displayed cytotoxic activity, leading investigators to tab it as a promising candidate for the development as a treatment option for patients with CEACAM5-positive tumors.1,3

“This drug in preclinical models has had very good efficacy,” Bunn said. “Tumor reduction—not only tumor stasis, but actually reduction in tumor size—[was observed] in this in vivo animal model.”

Tusamitamab ravtansine is under investigation in patients with solid tumors in a phase 1/2 trial (NCT02187848). Eligible adult patients must have locally advanced/metastatic solid tumors that expressed or are likely to express CEACAM5 and have an ECOG performance status of 1 or less.

In the dose-escalation phase 1 portion of the trial, 31 patients received tusamitamab ravtansine at doses ranging from 5 to 150 mg/m², given every 2 weeks intravenously (IV). The dose-limiting toxicity of reversible grade 3 microcystic keratopathy was reported in 3 of the 8 patients who received tusamitamab ravtansine 120 mg/m² and in 2 of the 3 patients who were treated at 150 mg/m². Investigators determined the maximum tolerated dose (MTD) of tusamitamab ravtansine to be 100 mg/m² IV every 2 weeks.1

As of January 2020, ninety-two patients were treated at the MTD in the nonsquamous NSCLC cohort of the trial. Twenty-eight of these patients were moderate expressors of CEACAM5 (IHC ≥ 2+ on 1%-50% of tumor cells) and 64 were high expressors (IHC ≥ 2+ on ≥ 50% of tumor cells). The median age of the treated patients was 62.5 years (range, 31-91) and the median number of prior lines of therapy for advanced disease was 3 (range, 1-10). Most patients were men (51.1%) and most had undergone treatment with tusamitamab ravtansine for at least 12 months as of December 2021.6

Findings showed that 24 patients were treated for at least 6 months, 15 patients for at least 9 months, 11 patients for at least 12 months, 6 patients for at least 24 months, and 2 patients for at least 42 months (FIGURE).5 Five patients remained on treatment at the data cutoff, 1 of whom has remained on treatment for over 52 months. Among patients who were treated for at least a year, the median duration of treatment was 26.6 months (range, 12.1-45.3). Patients in this cohort had a median age of 61 years (range, 41-91) and 81% had high CEACAM5 expression. The median number of prior regimens for advanced disease was 2 (range, 1-6), with 54.5% of patients having...
received prior anti-PD-1/PD-L1 therapy and 45.5% having received antitubulin therapy.⁶

Of the patients who experienced a PR in the January 2020 analysis (n = 15), PR was still reported in 67% of patients who were treated for at least 6 months, 53% of patients who were treated for at least 9 months, and 47% of patients who were treated for at least a year. Additionally, patients who were treated for at least a year had better ECOG performance status and underwent fewer prior treatment regimens compared with the overall group. PR was also found to occur regardless of CEACAM5 expression level in patients who received tusamitamab ravaltsine for at least a year.

In terms of safety, investigators noted that only 1 patient who was treated for at least 12 months was forced to discontinue treatment due to a TEAE, which was breast cancer. The most common TEAEs were corneal events; any-grade corneal TEAEs occurred in 73% of patients with 36% of these being grade 3 or greater. Treatment was delayed or the dose was reduced in 7 patients and no corneal TEAEs were deemed serious or led to treatment discontinuation.

Investigators concluded that heavily pretreated patients exhibited a durable and frequently sustained response to treatment with tusamitamab ravaltsine. They also concluded that further clinical development of the agent is therefore warranted.

A MULTITUDE OF TUSAMITAMAB RAVTANSINE TRIALS ARE NOW UNDERWAY

In response to the positive findings among patients with NSCLC and increased CEACAM5 expression who were treated with tusamitamab ravaltsine, multiple clinical trials are actively recruiting to further examine the safety and efficacy of the agent. These include the phase 3 CARMEN-LC03 trial (NCT04154956), the phase 2 CARMEN-LC04 trial (NCT04394624), and the phase 2 CARMEN-LC05 trial (NCT04524689).

In CARMEN-LC03, approximately 554 patients with nonsquamous NSCLC and a CEACAM5 expression of at least 2+ in a minimum of 50% of tumor cells will be randomly assigned 1:1 to receive either tusamitamab ravaltsine or the standard-of-care docetaxel. Patients in the tusamitamab ravaltsine arm will receive the agent at a dose of 100 mg/m² IV every 2 weeks and docetaxel will be given at a dose of 75 mg/m² IV every 3 weeks.⁷

The primary endpoints of the study are progression-free survival (PFS) by RECIST 1.1 criteria as assessed by an independent blinded review committee and overall survival. Secondary endpoints include ORR, duration of response, health-related quality of life, and safety.

CARMEN-LC04 will examine tusamitamab ravaltsine in combination with monoclonal antibody ramucirumab (Cyramza) in approximately 36 pretreated patients with nonsquamous NSCLC with high CEACAM5 expression. Ramucirumab will be given IV prior to the IV administration of tusamitamab ravaltsine every 2 weeks.⁷

The primary outcome in the safety run-in (part 1) will be to assess the tolerability of the combination and confirm the recommended dose of tusamitamab ravaltsine when it is given with ramucirumab. Part 2 will evaluate the antitumor activity of the combination, as well as safety, durability of response, PFS, pharmacokinetic profile, and immunogenicity.

Finally, CARMEN-LC05 will enroll approximately 96 patients with nonsquamous NSCLC and a CEACAM5 expression of at least 2+ in a minimum of 50% of tumor cells will be randomly assigned 1:1 to receive either tusamitamab ravaltsine or the standard-of-care docetaxel. Patients in the tusamitamab ravaltsine arm will receive the agent at a dose of 100 mg/m² IV every 2 weeks and docetaxel will be given at a dose of 75 mg/m² IV every 3 weeks.⁷

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Investigative Approaches Seek to Enhance Outcomes for Patients With CDK12-Mutant mCRPC

**DNA DAMAGE HOMOLOGOUS** recombination repair (HR) genotypic variants are not created equal. Patients with metastatic castration-resistant prostate cancer (mCRPC), whose disease harbors somatic mutations, including BRCA1, BRCA2, and ATM, have demonstrated response to PARP inhibitors such as olaparib (Lynparza) and rucaparib (Rubraca). However, for the approximately 5% of patients with CDK12 variants, outcomes have been limited.1

Descriptive analyses have detailed the unique genomic profiles of tumors with CDK12 mutations (FIGURE 1).2,3 For example, in an analysis of 4918 mCRPC tumors, 6.4% of samples were positive for CDK12 mutations. When investigators explored the genomic profiles of these tumors and compared them with the tumors of patients without CDK12 wild-type disease, differences were present. Among patients with CDK12 mutations, there were significantly fewer loss-of-function genomic alterations in TMRRSS2:ERG (P < .0001), TP53 (P < .0001), PSEN (P < .0001), ATM (P = .001), PIK3CA (P = .003), RAI1 (P = .02), BRCA2 (P < .0001), and APC (P = .002).2

Investigators noted that the lower frequencies of these genomic alterations were associated with homologous recombination defect and the mTOR pathway, signaling that platinum agents, PARP inhibitors, and PIK3CA, AKT, or mTOR inhibitors may have efficacy for these patients.2

Significantly higher frequencies of CCND1 (P < .0001), BRAF (P = .007), and ERBB2 (P < .001) were reported among patients with CDK12 mutations in addition to higher frequency of cell regulatory genes MDM2/A (P < .0001) and CDK6 (P = .002). Finally, investigators also observed that microsatellite instability-high status was more frequent in patients with CDK12 mutation-positive disease vs those without (6% vs 3%; P = .007). The median tumor mutational burden was the same between the cohorts at 2.5.

Finally, in terms of PD-L1 expression, low-positive expression (1%-49% staining) was more frequent among patients with CDK12-positive disease vs those without (18% vs 9%, respectively; P = .02). This finding signaled those patients with CDK12-positive disease may derive additional benefit from treatment with immune checkpoint inhibitors.2

Further expanding on this analysis, in a panel discussion presentation during the 2022 Genitourinary Cancers Symposium, Eric J. Small, MD, noted the limited efficacy of recently approved agents, including olaparib and rucaparib, for patients with CDK12 mutations.4,5

Olaparib was approved for patients with HR gene-mutated mCRPC based on data from the PROfound study (NCT02987543). The study included patients with BRCA1, BRCA2, and ATM mutations with progressive disease following treatment with an androgen-signaling inhibitor. Overall, results showed a significant advantage with olaparib (n = 162) compared with placebo (n = 83) with a radiographic progression-free survival (rPFS) of 7.4 months vs 3.6 months, respectively (HR, 0.35; 95% CI, 0.25-0.47; P < .001), overall survival of 19.4 months vs 14.7 months (HR, 0.69; 95% CI, 0.50-0.97; P = .02), and an overall response rate of 33% vs 2%.6,7

Although the study was not designed to assess each individual variant type, patients with a CDK12 mutation experienced a narrower advantage with olaparib compared with all patients in cohort A of the study; the HR was 0.74 (95% CI, 0.44-1.33).

Similarly, in the phase 2 TRITON2 study (NCT02952534), which led to the approval of rucaparib,5 patients with BRCA4 alterations derived significant benefit with the targeted agent in both rPFS and prostate-specific antigen (PSA) responses. However, for patients with a cooccurring CDK12 mutation, no patients demonstrated an objective response to PARP inhibitor therapy.4 “CDK12 variants result in interesting observations: genomic instability, focal tandem duplications, and increased predictive neoantigens,” Small said. “This raises the question of the utility of checkpoint inhibitors.” Small, who is codirector of the urologic cancer service and a genitourinary oncologist at the University of California, San Francisco, added that small retrospective studies have shown early signals of efficacy with this approach and that prospective studies are needed to validate their use.

Results of a retrospective analysis by Antonarakis et al showed that among 11 men who had a CDK12 mutation and received a PARP inhibitor, none had a PSA response. However, among 9 men who received a PD-1 inhibitor in the fourth- to sixth-line setting, 33.3% had a PSA response, and median PFS was 5.4 months. Therapies included pembrolizumab (Keytruda; n = 5) and nivolumab (Opdivo; n = 4).8

**THE FUTURE OF LOSS-OF-FUNCTION MUTATIONS**

Building on these data, investigators are seeking to harness the synergy of CDK4/6 inhibitors with anti-PD-1/PD-L1 agents for patients harboring the loss of function alterations of CDK12.9

Investigators in a phase 2 trial (NCT04751929) will evaluate the efficacy of the CDK4/6 inhibitor abemaciclib (Verzenio) and atezolizumab (Tecentriq) in patients with mCRPC who have received at least 1 line of prior therapy with an antiandrogen in the hormone-sensitive or castration-resistant setting (FIGURE 2).3,10 Patients must also be ineligible for taxane chemotherapy.

The study will primarily evaluate the dual inhibition among patients with unselected mCRPC. However, an exploratory single stage
cohort will evaluate abemaciclib monotherapy and the investigational combination among those with loss of function mutations in CDK12. Estimated enrollment is 54 patients in the randomized portion and 21 patients in the exploratory cohort.

Patients in the primary analysis will be randomly assigned 1:1 to receive either abemaciclib monotherapy taken orally twice daily or intravenous atezolizumab administered on day 1 of a 21-day cycle plus abemaciclib in stage 1 of the trial schema. An interim efficacy analysis will be performed before enrollment continues for stage 2 of the trial. In the exploratory cohort, atezolizumab monotherapy will be administered to 5 patients who will undergo Bayesian toxicity monitoring. An additional 16 patients will be enrolled to receive the combination treatment. An on-treatment biopsy will be taken at 6 weeks and treatment will continue until disease progression or intolerance across the cohorts.

The coprimary end points of the unselected cohort include PFS at 6 months using Prostate Cancer Working Group 3 consensus guidelines and objective response rate. At least 1 of 12 planned patients must meet either end point to initiate stage 2 of the trial. Meaningful clinical activity across the trial will be defined as at least 6 of 17 total patients meeting the PFS end point or at least 5 patients meeting the objective response rate end point. In the selected cohort, an additional primary safety end point is incidence of dose-limiting toxicities in patients receiving the combination regimen. Secondary end points include clinical benefit rate, duration of response, and overall survival in the unselected cohort, and safety in all arms. Exploratory end points following tumor biopsy include comparison of FoxP3/CD8 ratio in patients who receive abemaciclib vs abemaciclib plus atezolizumab. Additional biopsy-directed end points include the association of response and genomic alterations identified from tissue or circulating tumor–derived exosomes.

The trial is open for enrollment.

**REFERENCES**


**FIGURE 2. Unselected Analysis of CDK12-Positive mCRPC**.

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: Abemaciclib monotherapy (n = 12)</td>
<td>Arm A: Abemaciclib monotherapy (n = 15)</td>
</tr>
<tr>
<td>Arm B: Atezolizumab plus abemaciclib (n = 12)</td>
<td>Arm B: Atezolizumab plus abemaciclib (n = 15)</td>
</tr>
</tbody>
</table>

Unselected mCRPC: Randomly assigned 1:1

EXPLORATORY, SINGLE-STAGE COHORT

- mCRPC with CDK12 loss
- Arm C: Atezolizumab monotherapy (n = 5)
- Arm C: Atezolizumab plus abemaciclib (n = 16)

mCRPC, metastatic castration-resistant prostate cancer.
When metastatic pancreatic ductal adenocarcinoma (mPDAC) progresses on gemcitabine

Consider ONIVYDE + 5-FU/LV—the #1 prescribed and only FDA-approved regimen proven to extend overall survival in patients with mPDAC post-gemcitabine.

INDICATION
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.
Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
- Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.
- Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

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

WARNINGS AND PRECAUTIONS
- Severe Neutropenia: See Boxed WARNING. In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.
- Severe Diarrhea: See Boxed WARNING. Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed.
- Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.
- Severe Hypersensitivity Reactions: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.
- Embryo-Fetal Toxicity: ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.
WHAT COULD THE POSSIBILITY OF EXTENDED OS WITH ONIVYDE + 5-FU/LV MEAN FOR YOUR PATIENTS?

- 2 months longer median OS shown in NAPOLI-1: 6.1 months for ONIVYDE + 5-FU/LV (95% CI: 4.8, 8.5) vs 4.2 months for 5-FU/LV alone (95% CI: 3.3, 5.3); HR=0.68 (95% CI: 0.50, 0.93); log-rank p=0.014: a 32% reduction in risk of death

- The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia

*Based on data from Q4 2016 through Q3 2021.*
*NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE (70 mg/m² every 2 weeks) + 5-FU/LV was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional endpoints were progression-free survival and objective response rate.*

ADVERSE REACTIONS
- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)
- Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis
- Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia
- ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

DRUG INTERACTIONS
- Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

USE IN SPECIFIC POPULATIONS
- **Pregnancy and Reproductive Potential:** See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after ONIVYDE treatment
- **Lactation:** Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.


Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on adjacent pages.
ONIVYDE® (irinotecan liposome injection) for intravenous use
Initial U.S. Approval: 1996

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

INDICATIONS AND USAGE
ONIVYDE is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.
Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with S-FU/LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Severe diarrhea occurred in 13% of patients receiving ONIVYDE/S-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late-diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

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

WARNINGS AND PRECAUTIONS
Severe Neutropenia: ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE/S-FU/LV arm and 1/117 patients receiving single-agent ONIVYDE. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/S-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (S-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/S-FU/LV, and did not occur in patients receiving S-FU/LV. In patients receiving ONIVYDE/S-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (13/73 [55%] vs White patients [13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients. Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm³ or above. Reduce ONIVYDE dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles.

Severe Diarrhea: ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction). An individual patient may experience both early- and late-onset diarrhea.

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

Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive cough, fever, and chest pain. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

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

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

ADVERSE REACTIONS
The following adverse drug reactions are discussed in greater detail in other sections of the label:
- Severe Neutropenia
- Severe Diarrhea
- Interstitial Lung Disease
- Severe Hypersensitivity Reactions

Clinical Trials Experience
The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE 70 mg/m² with LV 400 mg/m² and S-FU 2400 mg/m² over 48 hours every 2 weeks (ONIVYDE/S-FU/LV; n=117), ONIVYDE 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and S-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by a 2 week rest (S-FU/LV; n=134). Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE/S-FU/LV arm, 9 weeks in the ONIVYDE monotherapy arm and 6 weeks in the S-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/S-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/S-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/S-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

Continued next page
Table 2: Adverse Reactions with Higher Incidence (≥5% Difference for Grades 1–4* or ≥2% Difference for Grades 3 and 4) in the ONIVYDE®/S-FU/LV Arm

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE/S-FU/LV n=117</th>
<th>S-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea‡</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis✓</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Intravenous catheter-related infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthnia</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
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<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Dehydration</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Cholinergic Reactions: ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

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

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

**DRUG INTERACTIONS**

**Strong CYP3A4 Inducers:** Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE therapy.

**Strong CYP3A4 or UGT1A1 Inhibitors:** Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., azatavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE therapy.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy, Risk Summary:** Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

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

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

**Females and Males of Reproductive Potential, Contraception, Females:** ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for 1 month after the final dose. **Males:** Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for 4 months after the final dose.

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

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

**OVERDOSAGE**

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

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When metastatic pancreatic ductal adenocarcinoma (mPDAC) progresses on gemcitabine

Consider ONIVYDE + 5-FU/LV—the #1 prescribed and only FDA-approved regimen proven to extend overall survival in patients with mPDAC post-gemcitabine1,2*

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WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
• Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment
• Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity

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

WARNINGS AND PRECAUTIONS
• Severe Neutropenia: See Boxed WARNING. In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients
• Severe Diarrhea: See Boxed WARNING. Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed
• Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD
• Severe Hypersensitivity Reactions: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction
• Embryo-Fetal Toxicity: ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment
WHAT COULD THE POSSIBILITY OF EXTENDED OS WITH ONIVYDE + 5-FU/LV MEAN FOR YOUR PATIENTS?

- 2 months longer median OS shown in NAPOLI-1: 6.1 months for ONIVYDE + 5-FU/LV (95% CI: 4.8, 8.5) vs 4.2 months for 5-FU/LV alone (95% CI: 3.3, 5.3); HR=0.68 (95% CI: 0.50, 0.93); log-rank p=0.014: a 32% reduction in risk of death†
- The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia²

*Based on data from Q4 2016 through Q3 2021.
†NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE (100 mg/m² every 3 weeks) or 5-FU/LV. After 83 patients were enrolled, a third arm, ONIVYDE (70 mg/m² every 2 weeks) + 5-FU/LV was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional endpoints were progression-free survival and objective response rate.²

ADVERSE REACTIONS
- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)
- Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; The most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis
- Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia
- ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

DRUG INTERACTIONS
- Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

USE IN SPECIFIC POPULATIONS
- Pregnancy and Reproductive Potential: See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after ONIVYDE treatment
- Lactation: Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.


Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on adjacent pages.
ONIVYDE® (irinotecan liposome injection) for intravenous use
Initial U.S. Approval: 1996

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

INDICATIONS AND USAGE
ONIVYDE is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.
Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU/LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Severe diarrhea occurred in 13% of patients receiving ONIVYDE/5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late-diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

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

WARNINGS AND PRECAUTIONS
Severe Neutropenia: ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients. Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below 1500/mm^3 or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm^3 or above. Reduce ONIVYDE dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles.

Severe Diarrhea: ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction). An individual patient may experience both early- and late-onset diarrhea.

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

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

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

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

ADVERSE REACTIONS
The following adverse drug reactions are discussed in greater detail in other sections of the label:
- Severe Neutropenia
- Severe Diarrhea
- Interstitial Lung Disease
- Severe Hypersensitivity Reactions

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

The most common adverse reactions (≥20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

Continued next page
Table 2: Adverse Reactions with Higher Incidence (≥5% Difference for Grades 1–4* or ≥2% Difference for Grades 3 and 4) in the ONIVYDE®/5-FU/LV Arm

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE/S-FU/LV n=117</th>
<th>S-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea‡</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis°</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Intravenous catheter-related infection</td>
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<td>3</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
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<td></td>
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<tr>
<td>Fatigue/asthensia</td>
<td>56</td>
<td>21</td>
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<tr>
<td>Pyrexia</td>
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<td><strong>Metabolism and nutrition disorders</strong></td>
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<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>4</td>
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<tr>
<td>Weight loss</td>
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<tr>
<td>Dehydration</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
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<tr>
<td>Alopecia</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Cholinergic Reactions: ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea. Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration, were reported in 3% of patients receiving ONIVYDE or ONIVYDE/S-FU/LV.

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

**DRUG INTERACTIONS**

Strong CYP3A4 Inducers: Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapeutics ±2 weeks prior to initiation of ONIVYDE therapy.

Strong CYP3A4 or UGT1A1 Inhibitors: Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, iraconazole, lopinavir, nefazodone, nefinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ±1 week prior to starting ONIVYDE therapy.

**USE IN SPECIFIC POPULATIONS**

Pregnancy, Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

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

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

Females and Males of Reproductive Potential, Contraception, Females: ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for 1 month after the final dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for 4 months after the final dose.

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

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

**OVERDOSAGE**

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

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Neoadjuvant Therapy Holds Promise for Patients With Locally Advanced Rectal Cancer

by MARIAM F. ESKANDER, MD, MPH

RESEARCH PUBLISHED IN 2022 has advanced our understanding of the effect of neoadjuvant therapy on organ preservation for patients with locally advanced rectal cancer. Prospective data support total neoadjuvant therapy and watch-and-wait approaches, with single-institution data on neoadjuvant immunotherapy for select patients with stage II or stage III rectal cancer.

Historically, the standard of care for locally advanced rectal cancer has been neoadjuvant chemoradiation and total mesorectal excision (TME), followed by adjuvant chemotherapy. Total neoadjuvant protocols, in which all chemotherapy is delivered up front (induction chemotherapy followed by chemoradiation or chemoradiation followed by consolidation chemotherapy), allow more patients to complete systemic therapy and treat potential micrometastatic disease earlier. According to National Comprehensive Cancer Network guidelines, total neoadjuvant therapy is the preferred regimen for all patients with locally advanced rectal cancer. Up to a quarter of patients will have a complete pathological response after total neoadjuvant therapy, raising the question of whether some can avoid morbid, life-altering operations.

PROOF IS IN THE NUMBERS

Data from the Organ Preservation in Rectal Adenocarcinoma (OPRA) trial (NCT02008656) were published in the Journal of Clinical Oncology in August 2022. This prospective, randomized trial was designed as 2 stand-alone phase 2 studies, the results of which were compared with historical data. Oncologic outcomes were assessed for patients with stage II or stage III rectal adenocarcinoma treated with total neoadjuvant therapy and selective watch-and-wait protocols vs TME based on tumor response. The primary end point was disease-free survival (DFS) and the secondary end point was TME-free survival. These data were compared with historical controls who received the standard neoadjuvant chemoradiation and TME. A total of 324 patients from 18 US institutions were randomly assigned to induction chemotherapy followed by chemoradiation (INCT-CRT; n = 158) or CRT followed by consolidation chemotherapy (CRT-CNCT; n = 166). Chemotherapy consisted of 4 months of 5-fluorouracil (5-FU) plus leucovorin or oxaliplatin or capecitabine and oxaliplatin; chemoradiation was 5000 to 5600 cGy combined with 5-FU or capcitabine.

Approximately three-quarters of the patients in each arm (71% in the INCT-CRT arm and 76% in the CRT-CNCT arm) had a complete clinical response or near-complete response and were offered watch-and-wait. At a median follow-up of 3 years, 40% of patients in the INCT-CRT arm and 27% in the CRT-CNCT arm developed tumor regrowth, and all were recommended for TME. Three-year DFS rates were comparable between the groups: 76% (95% CI, 69%-84%) in the INCT-CRT group and 76% (95% CI, 69%-83%) in the CRT-CNCT group, consistent with a 75% historic 3-year DFS rate. The 3-year TME-free survival rate, however, was superior for the CRT-CNCT group (53% [95% CI, 45%-62%]) compared with 41% (95% CI, 33%-50%) for the INCT-CRT group. These data show that a large proportion of patients are eligible for watch-and-wait and approximately half can achieve rectal preservation at 3 years without a reduction in survival. CRT-CNCT emerges as the preferred regimen for achieving organ preservation, although the sequence of chemoradiation and chemotherapy did not change DFS.

Most tumor regrowth events occurred within the 2 years of completion of neoadjuvant therapy. Importantly, patients who underwent TME after tumor regrowth had similar outcomes compared with those who underwent TME after initial restaging, suggesting that delaying surgery until tumor regrowth is not detrimental.

**FIGURE.** Phase 2 Trial Design for Dostarlimab in dMMR Rectal Cancer

![Phase 2 Trial Design for Dostarlimab in dMMR Rectal Cancer](image-url)
However, mismatch repair-deficient (dMMR) rectal cancers can be resistant to standard systemic therapy, with high rates of progression reported after neoadjuvant chemotherapy for locally advanced disease. A prospective phase 2 study (NCT04165772), data from which were published in the New England Journal of Medicine in June 2022, evaluated a single-agent anti–PD-1 monoclonal antibody in the neoadjuvant setting for this population. In this single-institution study, 16 patients with dMMR stage II or stage III rectal adenocarcinoma received single-agent dostarlimab-gxly (Jemperli) every 3 weeks for 6 months. There were no adverse events of grade 3 or higher. Most patients showed no viable tumor on biopsy at 6 weeks. There were no adverse events of grade 3 or higher.

This study suggests that anti–PD-1 blockade is more effective for locally advanced rectal tumors than it has been for metastatic colorectal cancer. This could obviate the need for chemoradiation, chemotherapy, and surgery in the 5% to 10% of patients with rectal cancer with dMMR tumors. The durability and reproducibility of this data remain to be seen.

**THE ROLE OF SURVEILLANCE**

Both studies highlight that close surveillance is paramount for patients with a complete clinical response who do not undergo surgical management. The methods for assessment of clinical complete response in the rectum include endoscopy, digital rectal examination, and imaging. In OPRA, patients were restaged within 8 weeks (± 4 weeks) of completing total neoadjuvant therapy and reassessed with digital rectal exam and flexible sigmoidoscopy every 4 months for the first 2 years and every 6 months for the next 3 years. Rectal MRI was performed every 6 months for the first 2 years and annually for the next 3 years. CT scans of the chest/abdomen/pelvis to assess for metastasis were performed at least once per year.

In the immunotherapy trial, patients underwent endoscopy with biopsy; digital rectal exam, MRI of the rectum; 18F-fluorodeoxyglucose positron emission tomography; and CT of the chest, abdomen, and pelvis every 4 months after completion of treatment. These new neoadjuvant paradigms can transform the way we treat locally advanced rectal cancer, making organ preservation and the resulting benefits in quality of life a reality for more patients for longer periods. Ongoing studies will help us hone patient selection and understand the long-term implications of these changes.

**MORE FROM OUR PARTNER**

Unraveling of Genetic Mechanism Behind Tumor Formation May Improve Targeted Treatment for Patients With Cancer

Genetic alterations in the FGFR2 gene occur in various cancer types and represent a promising target for therapies. However, clinical responses to available therapies remained variable and unpredictable, making it difficult to select patients who would benefit from these types of treatments. An international team of investigators, including Shridar Ganesan, MD, PhD, chief of molecular oncology and associate director for translational research at Rutgers Cancer Institute of New Jersey, have found new opportunities to improve diagnostics and targeted therapy for many patients with cancer.

Read the full release at OncLive.com: bit.ly/3crzqPK
Hematologic adverse reactions

- Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) is confirmed. It had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

- 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.
**In the PRIMA trial:**

**More than 2X PFS vs placebo in HRd PATIENTS**

**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 leucocytes (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%).

**Please see Brief Summary on the following pages.**


Visit [ZEJULAHCP.COM](https://www.ZEJULAHCP.COM) to explore the PRIMA data.

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**Reduction in Risk of progression or death with ZEJULA vs placebo**

HR, 0.43 (95% CI, 0.31-0.59) **P<0.0001**

**Reduction in Risk of progression or death with ZEJULA vs placebo**

HR, 0.62 (95% CI, 0.50-0.76) **P<0.0001**

<table>
<thead>
<tr>
<th>MEDIAN PFS IN THE HRd POPULATION</th>
<th>21.9 months ZEJULA <strong>57%</strong> reduction vs 10.4 months placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDIAN PFS IN THE OVERALL POPULATION</td>
<td>13.8 months ZEJULA <strong>38%</strong> reduction vs 8.2 months placebo</td>
</tr>
</tbody>
</table>

ZEJULA demonstrated significantly longer median PFS vs placebo in the overall population.
Cancer is associated with homologous recombination deficiency (HRD) positive status defined by either: a deleterious or suspected deleterious BRCA mutation, or a germline instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy.

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

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies
ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose disease has progressed. ZEJULA is indicated for the treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received previous chemotherapy and have disease that has progressed.

2 First-Line Maintenance Treatment of Advanced Ovarian Cancer
In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 4% 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 15 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

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

4 First-Line Maintenance Treatment of Advanced Ovarian Cancer
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.

5 Hypertension and Cardiovascular Effects
In QUADRA, 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 and for 6 months after the last dose of ZEJULA. Discontinue ZEJULA for hypertension if therapy is not controlled. In QUADRA, ≥ Grade 3 hypertension, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients receiving ZEJULA. Discontinuation due to hypertension occurred in 0.4% of patients.

6 Hypertension and Cardiovascular Effects
In PRIMA, ≥ Grade 3 hypertension, anemia, and neutropenia occurred in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to hypertension, anemia, and neutropenia occurred in 29%, 25%, and 20%, respectively, of patients.

7 Hypertension and Cardiovascular Effects
In NOVA, ≥ Grade 3 hypertension, anemia, and neutropenia were reported in 28%, 27%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to hypertension, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients.

8 Hypertension and Cardiovascular Effects
Discontinue ZEJULA until patients have recovered from hematologic toxicity caused by previous chemotherapy (≥ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematologic toxicities do not resolve within 28 days following interruption, discontinue ZEJULA and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) for full prescribing information).

9 Hypertension and Cardiovascular Effects
In QUADRA, ≥ Grade 3 thrombocytopenia, anemia, and neutropenia occurred in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 26%, 23%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 15 patients (0.8%).

10 Hypertension and Cardiovascular Effects
In QUADRA, ≥ Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 16%, 15%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 11%, 10%, and 8%, respectively, of patients.

11 Hypertension and Cardiovascular Effects
In QUADRA, ≥ Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 28%, and 27%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 13%, 12%, and 11%, respectively, of patients.

12 Hypertension and Cardiovascular Effects
In QUADRA, ≥ Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 27%, 26%, and 25%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 11%, 10%, and 9%, respectively, of patients.
Patients receiving ZEJULA with dose based on baseline weight or platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (8%) and anemia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% 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 and Table 4 summarize adverse reactions and abnormal laboratory findings in the groups of patients who received ZEJULA.

**Table 3: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA**

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>AST/ALT increase</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
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<tr>
<td>Creatinine decrease</td>
<td>10</td>
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<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</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%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

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

**Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA Cont’d**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
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<td>20</td>
<td>12</td>
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<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
<td>12</td>
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</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 transpeptidase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, and eosinophilia.

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

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
<td>10</td>
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<td>12</td>
<td>20</td>
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<tr>
<td>AST/ALT increase</td>
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<tr>
<td>Creatinine decrease</td>
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<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
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<td>20</td>
</tr>
</tbody>
</table>

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in QUADRA, a single-arm study in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration of therapy was 4 months (range: 0.11 to 30 months).

Fatality adverse reactions occurred in 2% of patients, including cardiac arrest. Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in ≥3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%). Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (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.

**Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA in PRIMA**

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
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<tr>
<td>AST/ALT increase</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
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<tr>
<td>Creatinine decrease</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
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<td>20</td>
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<tr>
<td>AST/ALT increase</td>
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<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine decrease</td>
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<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA Cont’d**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
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<tr>
<td>AST/ALT increase</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine decrease</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Placebo</th>
<th>Placebo</th>
<th>ZEJULA</th>
<th>ZEJULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT elevation</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>AST/ALT increase</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine decrease</td>
<td>10</td>
<td>20</td>
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</tr>
<tr>
<td>Platelet count</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 7: Common Terminology Criteria for Adverse Events version 4.02**

- Includes neutropenia, neutrophil infection, neutrophil sepsis, and febrile neutropenia.
- Includes leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.
- Includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatinine increased.

**Table 8: Common Terminology Criteria for Adverse Events version 4.02**

- Includes preferred terms of neutropenic infection, neutrophil sepsis, and febrile neutropenia.

**Table 9: Common Terminology Criteria for Adverse Events version 4.02**

- Includes preferred terms of neutropenic infection, neutrophil sepsis, and febrile neutropenia.

---

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.*
Table 1: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4* (n=463) %</th>
<th>Grades 3-4* (n=463) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>0.2</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>Infections and infestations</td>
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<td></td>
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<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<td></td>
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<tr>
<td>Musculoskeletal pain</td>
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<td>3</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Insomnia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
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<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></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

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: Pancreatitis

Immune System Disorders: Hypersensitivity (including anaphylaxis).

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

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

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

Skin and Subcutaneous Tissue Disorders: Phototoxicity.

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 embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus.

The background risk for 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 or milk production. Because of the potential for serious adverse reactions in a 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

In PRIMA, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. In NOVA, 35% of patients were aged 65 years or older and 6% were aged 75 years or older. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mild (Ccr: 60 to 89 mL/min) to moderate (Ccr: 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 level of normal [ULN] to 3.0 x ULN and any aspartate transaminase [AST] level and any AST level or bilirubin ≥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 or bilirubin ≥ULN and AST>ULN).

17 PATIENT COUNSELING INFORMATION

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

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/ or laboratory findings of low blood cell counts or a need for blood transfusions. This may be a sign of hematological toxicity or MDS or AML, which has been reported in patients treated with ZEJULA [see Warnings and Precautions (5.1)].

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 (8.3)].

Allergic Reactions to 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)].

8 USE IN SPECIFIC POPULATIONS

Hypertension and Cardiovascular Effects

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 (8.3)].

Allergic Reactions to 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)].

ZIC:LBRS 03/2021

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NRPJRNA220001 March 2022

Produced in USA.
AI-Powered Focal Therapy Maps Future Treatment Paradigm in Prostate Cancer

by Kyle Doherty

For clinicians tasked with treating patients with prostate cancer, disease visualization has traditionally consisted of imprecise techniques such as MRI. However, a new artificial intelligence (AI)-based approach being developed by Avenda Health is poised to potentially revolutionize the treatment landscape in the field.

The iQuest system is a patient management software that uses AI and deep learning technology to map a patient’s prostate cancer, aiding clinicians in identifying the extent of a patient’s disease. It is meant to be paired with their proprietary FocalPoint laser ablation system, which is designed to treat localized prostate cancer under local anesthesia. Avenda believes that this dual approach can lead to improved outcomes for patients with prostate cancer with preserved quality of life.

“Prostate cancer is unique, as it is one of the only solid cancers we cannot image very well,” Brittany Berry-Pusey, PhD, cofounder and chief operating officer of Avenda Health in Los Angeles, California, said in an interview with OncologyLive®. “On an MRI alone, radiologists can identify hot spots, but they cannot tell you exactly where the cancer is. The only way we can truly diagnose is through biopsies. [With the iQuest system], we have taken all these data—we use the MRI images, biopsy information, and pathology reports—to create a cancer probability map. We [calculate] voxel-level probability of clinically significant prostate cancer, and we help the physician identify cancer margins.”

The FocalPoint laser ablation system, also known as the Orion System, is designed to deliver targeted treatment via laser ablation and preserve the patient’s urinary and sexual function as much as possible. Using ultrasound guidance, a laser needle and sensor are inserted into the target tissue, and the needle is then heated, leading to coagulation necrosis. The system also allows the clinician to monitor tissue temperature and treatment progress in real time.

On May 11, 2021, the FDA granted breakthrough device designation to Avenda Health for a lumpectomy product, which was eventually developed into the FocalPoint system. The designation was partially based on the results of a phase 1 trial (NCT04305925) of 10 patients, showing the system was safe and resulted in no decline in urinary or sexual function.

More recently, in August 2022, the FDA awarded an investigational device exemption to the FocalPoint system powered by iQuest. “It is unfortunate that 50% of men with prostate cancer will have urinary or sexual dysfunction caused by their therapy,” Berry-Pusey said. “We have better solutions for these patients and [can] treat their prostate cancer [and] preserve their quality of life. That is the promise of iQuest and FocalPoint.”

iQuest Guides FocalPoint to Impressive Results

In May 2022, Priester et al presented 2 abstracts on behalf of Avenda Health at the Engineering and Urology Society 35th Annual Meeting in New Orleans, Louisiana, that demonstrated the efficacy of the iQuest system and that of the FocalPoint technique in patients with prostate cancer.

The first abstract outlined the development and validation of the iQuest system. The machine learning algorithm estimates voxel-level risk of clinically significant prostate cancer and produces a 3-dimensional lesion heat map. Investigators also used whole-mount prostatectomy data to develop a novel metric, the Marks Confidence Score, that correlates the lesion heat maps with the probability of encapsulating all clinically significant prostate cancers. This ultimately aids clinicians in identifying favorable candidates for focal therapy and estimating the efficacy of proposed treatment margins.

The model was developed using data from 875 patients from multiple institutions. Study authors input T2-weighted MRI data, surface models of the prostate, Prostate Imaging Reporting & Data System regions of interest, and tracked biopsy cores. The algorithm created lesion heat maps for 50 whole-mount prostatectomy cases, and a second set of 50 whole-mount prostatectomy findings from an outside institution were used for comparison to validate the Marks Confidence Scores.

For each case the area under the Marks Confidence curve was calculated by plotting Marks Confidence Score vs margin volume. The study authors hypothesized that patients with a high area under the Marks Confidence curve (≥ 0.6) would be favorable candidates for focal therapy.

Investigators found no significant differences between the observed clinically significant prostate cancer encapsulation rate compared with the rate predicted by the Marks Confidence Score (P = .099). The median error rate was 2% (IQR, 0%-6%). The average margin volume for clinically significant prostate cancer encapsulation was lower for patients deemed as favorable candidates for focal therapy (n = 24) compared with those who were unfavorable candidates (n = 26), at 31% and 52%, respectively (P = .001).

In the second abstract, Priester et al leveraged the iQuest system to generate treatment margins and compared the margins with those produced by the standard-of-care methodology. The standard-of-care techniques consisted of hemi-gland margins or a 10-mm isotropic expansion of MRI-visible regions of interest.

The machine learning margin models improved sensitivity for clinically significant prostate cancer...
TABLE. Efficacy of iQuest System in Defining Prostate Cancer Focal Therapy Treatment Margins

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hemi-gland margins</th>
<th>10-mm ROI expansion</th>
<th>iQuest margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sensitivity</td>
<td>94.1%</td>
<td>93.2%</td>
<td>96.9%</td>
</tr>
<tr>
<td>P = .01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean specificity</td>
<td>53.9%</td>
<td>63.4%</td>
<td>51.2%</td>
</tr>
<tr>
<td>P = .51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encapsulation</td>
<td>56%</td>
<td>74%</td>
<td>80%</td>
</tr>
<tr>
<td>P = .01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROI, region of interest.

10-mm region of interest; however, the difference was not statistically significant (TABLE).

"If we have the end goal of treating just the cancerous lesions [and] leaving the healthy prostate intact, which is the goal of focal therapy in general, you need to know where the cancer is," Berry-Pusey said. "iQuest helps with identifying where the cancer truly is, [then], now that we know where the cancer is, we can treat just the cancerous lesions [with FocalPoint] leaving the rest of the healthy prostate intact." Additionally, Priester et al presented another related study at the meeting that highlighted an automated method that could be used for ablation site placement for a variety of treatment modalities, including the FocalPoint system. Study authors wrote an algorithm in Python that was designed to be a modality-agnostic method for ablation site selection.

The algorithm required the locations of the interstitial treatment applicators to be inputted as points of origin. Three-dimensional surfaces for the prostate, region of interest, margin intended for treatment, and ablation volume were also required.

Investigators tested the algorithm on 11 unilateral and 6 bilateral margins collected from 11 patients who had previously undergone focal treatment for prostate cancer. They measured margin encapsulation of the ablation volume aggregate for 18 versions of ablation volume size and shape. Size was measured in transverse diameters (12 mm, 18 mm, and 26 mm) and the tested geometry consisted of spheres, ellipses,

Most Patients Approve of AI Aiding Diagnosis or Treatment Plan

by TODD SHRYOCK

A SURVEY APPEARING IN JAMA Network Open found that among 926 respondents, 66% considered artificial intelligence (AI) playing a big role in their diagnosis or treatment as very important, with 29.8% rating AI use as somewhat important. However, not all patients were comfortable with AI playing a big part in their health care.

Of those surveyed, 31% said AI usage made them very uncomfortable and another 40.5% were somewhat uncomfortable receiving a diagnosis from an AI algorithm that was accurate 90% of the time but incapable of explaining its rationale. Overall, most patients believe AI would make health care much better (10.9%) or somewhat better (44.5%) compared with 4.3% who thought it would make it somewhat worse or much worse (1.9%). The remaining 19% did not know one way or the other.

Comfort levels varied depending on which application AI was being applied to. For example, 55% of patients were either very or somewhat comfortable with AI reading chest radiographs, but that number dropped to 31.2% when the task was making a cancer diagnosis.

Most respondents were concerned about misdiagnosis (91.5%), privacy breaches (70.8%), less time with clinicians (69.6%), and higher costs (68.4%; FIGURE). Respondents who identified as racial or ethnic minorities ranked these issues higher than White respondents.

READ THE FULL STORY

bit.ly/3AhSOqf

FIGURE. Patient Concerns on Artificial Intelligence in Health Care

- Misdiagnosis
- Privacy breaches
- Less time with clinicians
- Higher costs
capsules, cubes, prims, and custom shapes for a total of 306 unique instances that were evaluated.

Findings from the study showed that the algorithm took an average of 2.25 seconds (range, 0.4-6.5) to run to completion and placed an average of 11 ablation volumes (range, 1-41). The highest rate of mean coverage occurred in prism-shaped ablation volumes (99.1%), followed by cubes (98.8%), capsules (94.4%), custom shapes (91.6%), spheres (90.0%), and ellipses (89.1%). Mean margin coverage achieved with the algorithm was significantly higher compared with manual planning, 94% vs 87%, respectively ($P = .005$). Study authors concluded that this methodology could potentially be used to simplify the planning process for focal treatment of prostate cancer through the automation of ablation site placement.

**“EXCITING” FUTURE AWAITS**

The investigational device exemption from the FDA has paved the way for the iQuest and the FocalPoint systems to be used in tandem in a randomized, controlled clinical trial of patients with prostate cancer. The trial will compare the approach with the standard of care. Berry-Pusey noted that the trial will tackle the current primary limitation of the iQuest plus FocalPoint ablation approach, which is a lack of understanding of the exact superiority of the technology compared with current techniques in a controlled setting.

The upcoming trial was designed based on outcomes from workshops conducted by the FDA to determine the best approach to conduct a clinical trial in the particular field of prostate cancer, according to Berry-Pusey. The primary outcome measure will be progression-free survival.

“We really are excited for this trial—we think that this will be the marquee study in this field,” Berry-Pusey said. “[We believe that] iQuest and FocalPoint are the future of prostate cancer care. We are excited to get the data and the support of our clinical partners as we improve treatment options for men with prostate cancer.”

Berry-Pusey envisions the iQuest system moving upstream in the care pathway and being used more extensively as a patient management software. She also noted that the software will be able to help clinicians with risk stratification for each individual patient and aid in identifying more personalized treatment plans.

“The personalization that iQuest creates for each patient will help patients and physicians make better decisions about their care in the future,” she said.

**REFERENCES**


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Investigators Validate Role of Liquid Biopsy in Predicting Chromosomal Abnormalities in Myeloid Neoplasms

by ONCLIVE® STAFF

Clinical Perspectives | MYELOID NEOPLASMS

LIQUID BIOPSY USING TARGETED next-generation sequencing (NGS) for early diagnosis and monitoring of myeloid neoplasms in patients is effective and detects chromosomal structural abnormalities, according to a retrospective study conducted at Hackensack University Medical Center in New Jersey.1

Patients with myeloid neoplasms often undergo invasive testing, such as bone marrow biopsies, to obtain samples of viable cells for cytogenetic testing with a turnaround time of 7 to 14 days. Alternative options have been explored; however, methods such as fluorescence in situ hybridization, which can only detect 1 abnormality at a time; array technology, which requires significant quantity of samples to confirm accuracy; and whole-genome sequencing, which is expensive, have failed to overcome their associated pitfalls in this space.

To overcome these limitations, investigators leveraged NGS to evaluate chromosomal gain or loss in liquid biopsies of patients with myeloid neoplasms. “Our primary goal was risk-stratifying patients and to understand [whether] we could use these peripheral blood tests in place of more invasive testing; we found that...patients with high sensitivity and specificity were able to be detected if they had myeloid neoplasms; some even had lymphoid neoplasms,” lead author Andrew Ip, MD, explained.

In an interview with OncologyLive®, Ip discussed the importance of liquid biopsies in detecting myeloid neoplasms and risk-stratifying patients. Ip is chief of the Outcomes and Value Care Division and a member of the Division of Lymphoma at John Theurer Cancer Center, Hackensack University Medical Center, in New Jersey.

Ip described the targeted panel used in the study as having “close to 300 different types of DNA, mutation profiling, and up to approximately 1200 RNA expression detection, so it is much more comprehensive than some of the other tests that are usually done.”

The retrospective study included samples from March 2020 to September 2021 at the John Theurer Cancer Center and Hackensack University Medical Center in a sample size of 144 patients with a median age of 68.5 years (range, 24-96). There were 2821 plasma cell-free DNA samples from patients with confirmed or suspected myeloid or lymphoid neoplasm, which were sequenced for chromosomal gain or loss. The diagnoses at baseline included acute myeloid leukemia (AML; 22%), myelodysplastic syndrome (MDS; 34%), and myeloproliferative neoplasms (44%).

Describing the study, Ip said, “The idea here is to use liquid biopsies, essentially peripheral blood testing, and for this study we looked at copy number variation [to identify] cytogenetic differences.”

Of the 2821 examined samples, 54.5% had mutations consistent with the presence of neoplastic clones. Among these (n = 1539), 59% of samples had abnormalities associated with myeloid neoplasms, 16% of which had chromosomal structural abnormalities; 41% of samples were associated with lymphoid neoplasms, 12% of which had chromosomal abnormalities. The abnormalities were shown in mutations of at least 1 gene in all samples except 2 that had no demonstrable mutations. Further, the median variant allele frequency (VAF) was 8.09% (range, 0.002%-99.55%). Investigators noted that when VAF was detected at 13% or higher, samples were “associated with clear, detectable chromosomal structural abnormalities.”

Ip described the results as having “a pretty high sensitivity,” adding that “within the allele frequency, there is the VAF; this is detecting how much of the mutation is within the blood sample. For our study, 13% was the cutoff to detect copy number variations or chromosome structure abnormalities that would define AML or MDS.” Ip explained that other NGS liquid biopsy tests could get slightly different results, and that comparing different tests or using many tests in conjunction with each other is a next step in validating the research.

For example, in this study, findings from 89 liquid biopsy samples from patients with MDS or AML...
were compared with available bone marrow samples. The cytogenetic data were obtained within 2 weeks of the liquid biopsy sample. To conduct the comparison, investigators grouped the cytogenetic and chromosomal findings into 3 risk groups: poor, intermediate, and complex.

In terms of classification, the NGS chromosomal structural analysis and the bone marrow samples had 100% concordance.

“That means we were able to classify these patients 100% of the time based off their leukemia risk, as defined by the European Leukemia Network and other organizations,” Ip said. “That showed the power of this test. I think that is important for clinical implications.”

Other noted advantages of the NGS test included the turnaround time of 5 to 7 days, ability to allow for less invasive and less serial monitoring of patients, as well as the ability to circumvent hurdles with other tests including lack of circulating tumor cells and availability of bone marrow samples.

Gene selection for the NGS panel was also an advantage noted by the investigators, who wrote, “Genes were selected because they are involved in oncogenesis rather than because they are relevant to covering chromosomal regions. Therefore, these genes provided an important mutation profile in addition to detecting chromosomal abnormalities. Smaller panels may not cover all chromosomal regions that are important in hematologic neoplasms. The ability of such a panel to detect both mutations and chromosomal abnormalities is a highly cost-effective and clinically useful approach in evaluating molecular abnormalities in hematologic neoplasms.”

Ip discussed a possible pairing with Hackensack University Medical Center’s partner Georgetown University in Washington, DC, to conduct more research with a larger sample size.

Limitations of the study included the isolated chromosome abnormality, deletion 5q, which is a form of MDS that is not always detected by testing. Ip explained, “Deletion 5q is a rare case and [approximately] 95% to 99% of these patients will have some sort of molecular mutation profile that you can detect here.” Another drawback of liquid biopsies is that most insurance companies do not pay for the test. However, Ip said that is quickly changing. “Every month, at least in New Jersey, there seems to be more understanding that these tests are important for our patients.”

In discussing disadvantages of liquid biopsies, Ip said the abundance of data can be overwhelming to sort through. “I think this paper hopefully helps to [clarify] that patients could be risk-stratified with this sort of test.…” The top [takeaway] is how do you interpret the wealth of information, because if you have 275 potential genes that are mutated, and 20 of them come back as positive, what does that mean?”

There are also many different liquid biopsy tests available and “there’s no set standard for some of this and that’s frustrating for the clinician, and even for the research side, [as investigators] try to come together and ask: Is there 1 test that we can use and study?”

REFERENCE

>> What’s Next for Liquid Biopsy?

“There’s a lot of exciting things that we’re trying to do with this sort of genomics platform and big data analysis. We’re trying to use a similar platform of genomic testing but looking at RNA sequencing and liquid biopsies. This is something that’s more novel and is not well recorded or well used clinically right now. It’s something that we’re very interested in the genomics laboratory with Maher Albitar, MD. [Using data from RNA sequencing] could provide more information on fusion abnormalities, cytokine profiling, and/or immune inflammatory profiling.

I think [clinicians] in the cancer space understand that immunotherapy is better than chemotherapy for a lot of patients. In general, the tumor microenvironment—that is, the immune environment around these tumors or cancers—is very important in understanding how a disease works and how patients are going to respond to treatment. We are trying to use the same [next-generation sequencing] platform to look at immunophenotyping and immune cytokine profiling. For example, we’re looking at the incidence of graft-vs-host disease, which is a morbid complication after allogeneic stem cell transplant; [we want to know] how you can predict that.” —Andrew Ip, MD

For more from Ip, and to learn about the ongoing personalized medicine efforts at John Theurer Cancer Center, visit: bit.ly/3PRrl4m

For more information on OncClub, please contact: Kristi Rosa | Managing Editor, OncLive® | KRosa@OncLive.com

OncCLUB Join the Chat on Trending Trials in Cancer

Vol. 23 | No. 17 | SEPTEMBER 2022 63
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Indication

VONJO™ (pacritinib) is indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]) myelofibrosis (MF) with a platelet count below $50 \times 10^9/L$.

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

VONJO is available as 100 mg capsules, for oral use.

Important Safety Information

CONTRAINDICATIONS

VONJO is contraindicated in patients concomitantly using strong CYP3A4 inhibitors or inducers as these medications can significantly alter exposure to pacritinib, which may increase the risk of adverse reactions or impair efficacy.

Please see Important Safety Information and Brief Summary on the following pages and full Prescribing Information at VONJO.com.


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Important Safety Information (cont.)

WARNINGS AND PRECAUTIONS

Hemorrhage: Serious (1%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <100 x 10^9/L. Serious (13%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <50 x 10^9/L. Grade 3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively. Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures. Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention. In the case of severe bleeding, hold VONJO until hemorrhage resolves. When the bleeding has resolved, restart treatment at 50% of the last given dose. If the bleeding recurs, discontinue treatment with VONJO. In the event of life-threatening bleeding, discontinue VONJO.

Diarrhea: VONJO caused diarrhea in approximately 48% of patients compared to 15% of patients treated with the control arm. The median time to resolution in VONJO-treated patients was 2 weeks. The incidence of reported diarrhea decreased over time with 41% of patients reporting diarrhea in the first 8 weeks of treatment, 15% in Weeks 8-16, and 8% in Weeks 16-24. Diarrhea resulted in treatment interruption in 3% of VONJO-treated patients. None of the VONJO-treated patients reported diarrhea that resulted in treatment discontinuation. Serious diarrhea adverse reactions occurred in 2% of patients treated with VONJO compared to none in the control arm. Control preexisting diarrhea before starting VONJO treatment. Manage diarrhea with anti-diarrheal medications, fluid replacement, and dose modification. Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms. Interrupt or reduce VONJO dose in patients with significant diarrhea despite optimal supportive care. In patients with Grade 3 or 4 diarrhea, hold VONJO until it resolves to Grade ≤1 or baseline, and restart VONJO at the last given dose. Intensity antidiarrheal regimen and provide fluid replacement. For recurrent diarrhea, hold VONJO until the diarrhea resolves to Grade ≤1 or baseline, and restart VONJO at 50% of the last given dose once the toxicity has resolved. Concomitant antidiarrheal treatment is required for patients restarting VONJO.

Thrombocytopenia: VONJO can cause thrombocytopenia. VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting moderate to severe thrombocytopenia (platelet count <100 x 10^9/L). VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting severe thrombocytopenia (platelet count <50 x 10^9/L). Monitor platelet count prior to VONJO treatment and as clinically indicated during treatment. Interrupt VONJO in patients with clinically significant worsening of thrombocytopenia that lasts for more than 7 days. Restart VONJO at 50% of the last given dose once the toxicity has resolved. If toxicity recurred, hold VONJO. Restart VONJO at 50% of the last given dose once the toxicity has resolved. Prolonged QT Interval: VONJO can cause prolongation of the QTc interval. QTc prolongation of >500 msec was higher in VONJO-treated patients than in patients in the control arm (1.4% vs 1%). QTc increase from baseline by 60 msec or higher was greater in VONJO-treated patients than in control arm patients (1.9% vs 1%). Adverse reactions of QTc prolongation were reported for 3.8% of VONJO-treated patients and 2% of control arm patients. No cases of torsades de pointes were reported. Avoid use of VONJO in patients with a baseline QTc of >480 msec. Avoid use of drugs with significant potential for QTc prolongation in combination with VONJO. Correct hypokalemia prior to and during VONJO treatment. Manage QTc prolongation using VONJO interruption and electrolyte management. In the case of QTc prolongation >500 msec or >60 msec from baseline, hold VONJO. If QTc prolongation resolves to ≤480 msec or baseline within 1 week, restart VONJO at the same dose. If time to resolution is >1 week, restart VONJO at a reduced dose. Major Adverse Cardiac Events (MACE): Another Janus associated kinase (JAK) inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis: Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies: Another JAK inhibitor has increased the risk of lymphoma and other malignancies, excluding non-melanoma skin cancer (NMSC), (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Risk of Infection: Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting therapy with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

DRUG INTERACTIONS

Effect of Other Drugs on VONJO: VONJO is predominantly metabolized by CYP3A4. Coadministration of VONJO with strong CYP3A4 inhibitors or inducers are contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

Effect of VONJO on Other Drugs: VONJO is an inhibitor of CYP1A2, CYP3A4, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter 1 (OCT1) in vitro. Concomitant administration of VONJO with these substrates may increase their plasma concentrations. Avoid coadministration of VONJO with drugs that are sensitive substrates of CYP1A2, CYP3A4, P-gp, BCRP, or OCT1.

ADVERSE REACTIONS

Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with best available therapy (BAT). The fatal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningorrhagia, and acute myeloid leukemia in <1% of patients each, respectively. Serious adverse reactions occurred in 47% of patients treated with VONJO 200 mg twice daily and in 31% of patients treated with BAT. The most frequent serious adverse reactions occurring in ≥3% patients receiving VONJO 200 mg twice daily were anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%), and squamous cell carcinoma of skin (3%). Permanent discontinuation due to an adverse reaction occurred in 15% of patients receiving VONJO 200 mg twice daily compared to 12% of patients treated with BAT. The most frequent reasons for permanent discontinuation in ≥2% of patients receiving VONJO 200 mg twice daily included anemia (3%) and thrombocytopenia (2%). The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no available data on VONJO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. Consider the benefits and risks of VONJO for the mother and possible risks to the fetus when prescribing VONJO to a pregnant woman.

Lactation: There are no data on the presence of pacritinib in either human or animal milk, the effects on the breastfed child, or the effects on milk production. It is not known whether VONJO is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with VONJO, and for 2 weeks after the last dose.

Infertility: Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib may impair male fertility in humans.

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

Hepatic Impairment: Administration of a single dose of VONJO 400 mg to subjects with hepatic impairment resulted in a decrease in the geometric mean area under the concentration curve (AUC) of pacritinib by 85%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C], respectively, compared to subjects with normal hepatic function. Avoid use of VONJO in patients with moderate [Child-Pugh B] or severe hepatic impairment (Child-Pugh C).

Renal Impairment: Administration of a single dose of VONJO 400 mg to subjects with renal impairment resulted in approximately 30% increase in maximal concentration (C_{max}) and AUC of pacritinib in subjects with eGFR 15 to 29 mL/min and eGFR <15 mL/min on hemodialysis compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use of VONJO in patients with eGFR ≤30 mL/min.

Please see Brief Summary on the following pages and full Prescribing Information at VONJO.com.

US-PAC-2000045 02/2022
VONJO™ (pacritinib) capsules, for oral use
Initial U.S. Approval: 2022

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

1 INDICATIONS AND USAGE
VONJO™ (pacritinib) is indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]) myelofibrosis (MF) with a platelet count below 50 x 10^9/L.

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

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage of VONJO is 200 mg orally twice daily, with or without food. Swallow capsules whole. Do not open, break, or chew capsules.

Patients who are on treatment with other kinase inhibitors before the initiation of VONJO must taper or discontinue according to the prescribing information for that drug.

4 CONTRAINDICATIONS
VONJO is contraindicated in patients concomitantly using strong CYP3A4 inhibitors or inducers as these medications can significantly alter exposure to pacritinib, which may increase the risk of adverse reactions or impair efficacy.

5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Serious (11%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <800 x 10^9/L. Serious (13%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <50 x 10^9/L. Grade ≥3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively.

Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures. Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention.

5.2 Diarrhea
VONJO caused diarrhea in approximately 48% of patients compared to 15% of patients treated with the control arm. The median time to resolution in VONJO-treated patients was 2 weeks. The incidence of reported diarrhea decreased over time with 41% of patients reporting diarrhea in the first 8 weeks of treatment, 15% in Weeks 8-16, and 8% in Weeks 16-24. Diarrhea resulted in treatment interruption in 3% of VONJO-treated patients with platelet counts <50 x 10^9/L. Grade ≥3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively.

Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures. Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention.

5.3 Thrombocytopenia
VONJO can cause worsening thrombocytopenia. VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting moderate to severe thrombocytopenia (platelet count <100 x 10^9/L). VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting severe thrombocytopenia (platelet count <50 x 10^9/L). Monitor platelet count prior to VONJO treatment and as clinically indicated during treatment. Interrupt VONJO in patients with clinically significant worsening of thrombocytopenia that lasts for more than 7 days. Restart VONJO at 50% of the last given dose once the toxicity has resolved. If toxicity recurs, hold VONJO. Restart VONJO at 50% of the last given dose once the toxicity has resolved.

5.4 Prolonged QT Interval
VONJO can cause prolongation of the QTc interval. QTc prolongation of >500 msec was higher in VONJO-treated patients than in patients in the control arm (1.4% vs 1%). QTc increase from baseline by 60 msec or higher was greater in VONJO-treated patients than in control arm patients (19% vs 1%). Adverse reactions of QTc prolongation were reported for 3.8% of VONJO-treated patients and 2% of control arm patients. No cases of torsades de pointes were reported.

Avoid use of VONJO in patients with a baseline QTc of >480 msec. Avoid use of drugs with significant potential for QTc prolongation in combination with VONJO. Correct hypokalemia prior to and during VONJO treatment. Manage QTc prolongation using VONJO interruption and electrolyte management.

5.5 Major Adverse Cardiac Events (MACE)
Another Janus kinase (JAK) inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

5.6 Thrombosis
Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

5.7 Secondary Malignancies
Another JAK inhibitor has increased the risk of lymphoma and other malignancies, excluding non-melanoma skin cancer (NMSC), (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

5.8 Risk of Infection
Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting therapy with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

5.9 Interactions With CYP3A4 Inhibitors or Inducers
Co-administration of VONJO with strong CYP3A4 inhibitors or inducers is contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

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

- Hemorrhage [see Warnings and Precautions (5.1)]
- Diarrhea [see Warnings and Precautions (5.2)]
- Thrombocytopenia [see Warnings and Precautions (5.3)]
- Prolonged QT Interval [see Warnings and Precautions (5.4)]
- Major Adverse Cardiac Events [see Warnings and Precautions (5.5)]
- Thrombosis [see Warnings and Precautions (5.6)]
- Secondary Malignancies [see Warnings and Precautions (5.7)]
- Risk of Infection [see Warnings and Precautions (5.8)]

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.
Table 5 summarizes the common adverse reactions in PERSIST-2 during randomized treatment.

### Table 5 Adverse Reactions Reported in ≥10% Patients Receiving VONJO (200 mg Twice Daily) or BAT During Randomized Treatment in PERSIST-2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VONJO (200 mg Twice Daily)</th>
<th>Best Available Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades/Grade ≥3</td>
<td>All Grades/Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48/4</td>
<td>16/0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34/32</td>
<td>13/0</td>
</tr>
<tr>
<td>Nausea</td>
<td>32/1</td>
<td>11/0</td>
</tr>
<tr>
<td>Anemia</td>
<td>24/22</td>
<td>15/14</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20/1</td>
<td>15/0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19/0</td>
<td>5/1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>15/1</td>
<td>5/0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10/3</td>
<td>3/0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12/5</td>
<td>13/1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10/0</td>
<td>9/3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10/2</td>
<td>6/0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10/0</td>
<td>6/0</td>
</tr>
<tr>
<td>Cough</td>
<td>8/2</td>
<td>10/0</td>
</tr>
</tbody>
</table>

a Grade by CTCAE Version 4.03.
8 USE IN SPECIFIC POPULATIONS (cont.)

8.1 Pregnancy (cont.)
In a pre- and post-natal development study in mice, pregnant animals were dosed with pacritinib from implantation through lactation at 30, 100, or 250 mg/kg/day. Maternal toxicity was noted at 250 mg/kg and associated with increased gestation length and dystocia, lowered mean birth weights and neonatal survival, and transiently delayed startle response, learning, and memory development at weaning.

8.2 Lactation
Risk Summary
There are no data on the presence of pacritinib in either human or animal milk, the effects on the breastfed child, or the effects on milk production. It is not known whether VONJO is excreted in human milk, because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with VONJO, and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential
Infertility
Males
Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib may impair male fertility in humans.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of VONJO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment
Administration of a single dose of VONJO 400 mg to subjects with hepatic impairment resulted in a decrease in the geometric mean AUC of pacritinib by 8.5%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C], respectively, compared to subjects with normal hepatic function. Avoid use of VONJO in patients with moderate [Child-Pugh B] or severe hepatic impairment [Child-Pugh C].

8.7 Renal Impairment
Administration of a single dose of VONJO 400 mg to subjects with renal impairment resulted in approximately 30% increase in C_{ss} and AUC of pacritinib in subjects with eGFR 15 to 29 mL/min and eGFR <15 mL/min on hemodialysis compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use of VONJO in patients with eGFR <30 mL/min.

17 PATIENT COUNSELING INFORMATION
See FDA approved patient labeling (Patient Information).
Discuss the following with patient prior to and during treatment with VONJO:
Current therapy with another kinase inhibitor
Advise patients who are currently taking a kinase inhibitor that they must taper or discontinue their current kinase inhibitor therapy according to the package insert for that drug prior to starting VONJO.

Hemorrhage
Advise patients that VONJO can cause hemorrhage and instruct them to consult their healthcare provider right away if bleeding occurs. Advise patients about how to recognize bleeding and of the urgent need to report any unusual bleeding to their physician. Patients should urgently seek emergency medical attention for any bleeding that cannot be stopped.

Diarrhea
Advise patients that VONJO can cause diarrhea. Advise patients to stay hydrated while taking VONJO and to inform their physician if they experience diarrhea. Instruct patients to initiate anti-diarrheal medications (eg, loperamide) if diarrhea occurs. Advise patients to urgently seek emergency medical attention if diarrhea becomes severe.

Thrombocytopenia
Advise patients that VONJO is associated with thrombocytopenia, and of the need to monitor complete blood counts before and during treatment.

Prolonged QT Interval
Advise patients to consult their healthcare provider immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of arrhythmia. Advise patients with a history of hypokalemia of the importance of monitoring their electrolytes.

Major Adverse Cardiac Events (MACE)
Advise patients that events of MACE including myocardial infarction, stroke, and cardiovascular death, have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not indicated. Advise patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis
Advise patients that events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not indicated. Advise patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Secondary Malignancies
Advise patients, especially current or past smokers and patients with a known secondary malignancy (other than a successfully treated NMSC), that lymphoma and other malignancies (excluding NMSC) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not indicated.

Infections
Advise patients that treatment with another JAK inhibitor has increased the risk of serious infections in patients with myeloproliferative neoplasms and that serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Inform patients of the signs and symptoms of infection and to report any such signs and symptoms promptly.

Nausea and Vomiting
Advise patients that nausea and vomiting may occur during treatment with VONJO. Instruct them on how to manage nausea and vomiting and to immediately inform their healthcare provider if nausea/vomiting become severe.

Drug-Drug Interactions
Advise patients to inform their healthcare providers of all medications they are taking, including prescription and over-the-counter medications, vitamins, herbal products, and dietary supplements.

Dosing
Advise patients to take VONJO twice a day, with or without food or drink, at similar times each day. Instruct patients to swallow the VONJO capsules whole and not to open, break, or chew the capsules. Instruct patients that if they miss a dose of VONJO, to skip the dose and take the next dose when it is due and return to the normal schedule. Warn patients not to take 2 doses to make up for the missed dose. Instruct patients to discontinue VONJO 7 days prior to any surgery or invasive procedures (such as cardiac catheterization, coronary stenting, or varicose vein ablation) due to the risk of bleeding and to only restart VONJO on the instruction of their healthcare provider. Patients should not change or stop taking VONJO without first consulting their physician.

Lactation
Advise patients to avoid breastfeeding while taking VONJO and for 2 weeks after the final dose.

Additional information can be found at VONJO.com.

Manufactured and marketed by:
CTI BioPharma Corp.
3101 Western Ave #800
Seattle, WA 98121
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THE BIOLOGY OF MULTIPLE MYELOMA has an evolving role in guiding research efforts involving diagnostic and prognostic capabilities of available biomarkers and related molecular pathways.

"Myeloma cells often have genetic abnormalities, and we often think about them as primary abnormalities, which are seen at all stages of the disease," Shaji Kumar, MD, said during a recent OncLive Insights® program, a video editorial series featuring in-depth reports from leaders in oncology specialties.

Kumar was joined by Jonathan Kaufman, MD, to discuss recent advances in molecular biomarkers in multiple myeloma. "There is an unmet need in the entire field of myeloma right now," Kaufman said. "It would be great if we had a biomarker that signaled [which patients] can have a 3-drug induction therapy and not 4-drug, or that signals [who should receive] doublet maintenance vs single-agent maintenance ... We don’t know the answers to any of these questions and using a biomarker would be extremely helpful, once we develop that."

In the discussion, Kumar and Kaufman reviewed the advances with translocations (t) such as t(11;14), treating practices, and emerging markers in the field.

**KUMAR**

We have been using a fair number of biomarkers, and quite a few of them are evolving as well. Particularly, some of those biomarkers or the biological changes that we see in the myeloma cells have lent themselves to be predictive markers for responses and other therapies that are evolving.

**KAUFMAN**

Recurrent translocations such as t(11;14) and the less common t(6;14), occur where there’s translocation of the cyclin proteins with chromosome 14. What we know is that certain translocations are associated with high-risk disease. But we say that in a very broad way, without really understanding what we’re learning more about particularly in t(11;14).

For example, we’re getting to the point where we can have predictive medicine for patients who present with t(11;14), as they are much more likely to respond to BCL2 inhibition. Clinically, what we’ve used to date is venetoclax [Venclexta], a BCL2 inhibitor.

There are additional abnormalities in terms of copy number. Trisomies are the most common abnormality in myeloma. Uniquely, the trisomies have only happened in the odd chromosomes and are associated with a better prognosis or standard-risk disease. There is some evidence that patients with trisomy are more sensitive to the immunomodulatory agents lenalidomide [Revlimid] and pomalidomide [Pomalyst]. [Additionally], there are enough data that we really can solidly say that 1q abnormalities and 17p deletion [del(17p)] are associated with a higher-risk disease.

There is a lot of controversy within the field regarding how much del(17p) there has to be for a patient to be [stratified as] high risk. The [Intergroupe Francophone du Myelome] advocating that del(17p) is greater than 55% of plasma cells, and where TP53 sits on 17p [and] you have a complete abrogation of the apoptotic pathway. If you have loss in one and TP53 mutation in the other, that is associated with significantly worsened outcome and increased risk.

When we think about oncogenic pathways that are involved, MYC is commonly involved as it is proliferative. Another pathway that we’re learning more about in myeloma and gaining a better understanding of its particular biology in myeloma is the RAS pathway. There are a lot of different pathways that are abnormal and to date, we’ve only been able to use 1 as predictive in helping us decide what treatment to do, which brings us back to t(11;14).

Among the primary abnormalities, approximately 40% of patients have translocations that involve the immunoglobulin heavy chain region of chromosome 14, with approximately 5 other recurrent partner chromosomes. One is t(11;14), which can be seen in approximately 15% to 20% of patients with multiple myeloma. Outcomes for this subgroup of patients have been studied in detail and it appears that these patients have outcomes that are intermediate between those with trisomies, which are good prognostic markers, and high-risk markers such as t(4;14) or t(14;16).

When you look at patients with t(11;14), they tend to have fewer secondary abnormalities such as del(17p) in their evolution over time. This is a subgroup of patients who appear to have differential outcomes. There seem to be some fundamental biological differences as well. What we have shown is that when you look at these patients with t(11;14), the myeloma cells appear to be more B cell-like. They tend to express some of the proteins on the surface, such as CD20, that you often associate with B cells. Their plasma cells generally tend to be smaller and can be more lymphoid compared with the other plasma cells that we see in other groups. Additionally, these patients tend to have more bone disease compared with the other subtypes or subgroups in terms of genetics.

Even though patients may appear similar, it is good to represent different diseases based on the fundamental genetic abnormality that they have. This has implications in terms of how we treat these patients. Increasingly, we’re starting to look at the differential effects of the many drugs we have available for treating patients with myeloma. There have been studies looking at BCL2 inhibition strategies, starting with venetoclax, a drug specifically created to target BCL2, given the significant role that BCL2 plays across many types of malignancies.

As with other cancers, preclinical work has demonstrated that use of venetoclax is associated with activity in myeloma cells, particularly when the myeloma cells carry the (11;14). Phase 1 or 2 early trials have been able to show that in approximately one-third patients with relapsed multiple myeloma, venetoclax was able to induce a tumor response to therapy. When we looked at it in more detail, it was clear that the majority of these responses appear to happen...
Among patients who have the t(11;14). Furthermore, it appeared that among the patients with t(11;14) those with high levels of BCL2 expression appear to experience even more efficacy with venetoclax.

Based on preclinical data showing synergy, venetoclax was combined with dexamethasone for treatment of relapsed myeloma. It appears that the dexamethasone makes these cells more sensitive to an inhibitor to the BCL2 pathway.

When we treat myeloma cells with BCL2 inhibitors, we sometimes see other protective mechanisms, such as MCL1 expression, go up. Proteasome inhibitors such as bortezomib [Velcade] appear to have the capability of down regulating MCL1 through different mechanisms, which then allow that synergy to happen. Based on all the preclinical work and the results from phase 1 studies, the phase 3 BELLINI trial [NCT02755597] was designed to explore the activity of venetoclax plus bortezomib and dexamethasone. This was conducted in patients with relapsed multiple myeloma who had 1 to 3 prior lines of therapy. Approximately 300 patients were randomly assigned to bortezomib/dexamethasone or bortezomib/dexamethasone with venetoclax.

The addition of venetoclax improved the depth of response and the progression-free survival among the overall group compared with bortezomib/dexamethasone alone. Interestingly, the initial readout of the trial demonstrated that patients who received venetoclax had increased mortality. This was an intriguing finding, which led to several additional analyses of the data. What became very clear was that the activity of venetoclax in combination with bortezomib/dexamethasone was most pronounced in patients with t(11;14), as one could have surmised from that preclinical work and the early clinical trials.

In addition, even among patients with the high expression of BCL2, measured using gene expression studies, those patients appear to benefit from the use of venetoclax as well, even if they did not have t(11;14). The results of BELLINI allowed us to explore 2 different biomarkers—t(11;14) as detected by FISH [fluorescence in situ hybridization] used in the clinic all this time, but also the BCL2 expression, using gene expression studies, which are not yet approved and in the clinic at this time. Both biomarkers allowed us to identify a population of patients likely to benefit from venetoclax and allowed us to exclude a patient population where the addition of venetoclax could potentially lead to a negative effect on outcomes.

I think much has been learned from BELLINI, particularly the type of patients in whom the use of venetoclax will have a positive effect. As these assays become available, particularly the BCL2 expression assay, and venetoclax gets approved for multiple myeloma we will be able to use it in this patient population.

KAUFMAN [In development] are flow panels that identify a B-cell phenotype that can help differentiate myeloma cells that are sensitive to venetoclax, because as you mentioned, not all t(11;14) cells are sensitive, and although rare, some non-t(11;14) cells are sensitive. And so, a BCL2 assay or a flow panel can help us make that decision so we can have appropriate predictive medicine.

Going back to the laboratory, the concept that t(11;14) cells are a little bit more lymphoid-like [and have] a little like a B-cell phenotype, the hypothesis of combining venetoclax with daratumumab (Darzalex) was that the venetoclax was going to address the more B-cell phenotype of the plasma cell, and the daratumumab—the CD38 monoclonal antibody—would target the plasma cell component of it. We moved forward with the t(11;14) patient population in the phase 2 trial [NCT03314181] and the 3-drug combination of venetoclax/daratumumab/dexamethasone, which showed very high response rates.

There are also very good preclinical data of the combination of venetoclax and proteasome inhibitors, specifically carfilzomib [Kyprolis], venetoclax, and dexamethasone for patients who received 1 to 3 prior lines of therapy [NCT02899052]. Investigators were able to demonstrate safety of that regimen. The dose expansion in the trial was 800 mg venetoclax daily with 70 mg/m² of carfilzomib on days 1, 8, and 15 of a 28-day cycle, plus weekly dexamethasone,
and high response rates were observed in the 80% to 90% range. It is important remember that all of these patients had t(11;14). We have been involved in developing the story, really from the very beginning, of the phase 1 study and it’s an exciting story. There are other biomarkers in myeloma not looking at t(11;14) and the BCL2 story, I want to touch on some of those emerging biomarkers of other biology in myeloma.

KUMAR Certainly, t(11;14) has kicked off the interest in trying to understand the fundamental differences in biology between these different types of myeloma, so to speak. Hopefully, as more therapies are introduced, we can use the best drug for the most appropriate patient.

Results that we get from the whole-genome sequencing or the template sequencing studies on the tumor cells show that one of the most common findings is the mutations involving the KRAS or the NRAS gene, and maybe, though a bit smaller, a proportion of patients with BRAF mutations as well. MEK inhibitors are an intervention that could have significant effect for these patients, as we have had several studies demonstrate that you can eradicate or at least get rid of a significant proportion of the myeloma cells. We have taken these concepts 1 step forward and are currently enrolling the MyDRUG trial [NCT03732703], which is looking at various genetic abnormalities and trying to tailor therapy [FIGURE]. These are patients with prolapsed myeloma, who have functional high-risk disease, who get sequencing done and based on the predominant, underlying genetic mutation, they get assigned to a specific therapy. For example, if they have a RAS mutation or a BRAF mutation, they get assigned to cobimetinib, which is given for a couple of cycles alone, and then combined with a 3-drug combination: dexamethasone, ixazomib, and pomalidomide. The initial 2 cycles give us a good assessment whether this targeted approach is something that is worthwhile and at the same time recognizing the fact that just targeting 1 abnormality is probably not sufficient for long-term disease control. Thus, we are adding a combination on top of the targeted agent. For those with t(11;14) they get assigned to the venetoclax, dexamethasone, ixazomib, and pomalidomide arm.

Some of these emerging biomarkers are helping us decide how best to approach the treatment of myeloma in each patient. There are several other biomarkers that are being developed, too. There’s a lot of interest in circulating tumor DNA, but it is early days for that in the myeloma space.

Dr Kaufman, what are your thoughts in terms of some of the best of these biomarkers that are already in the clinic that you’re using, and some of the new ones that are evolving?

KAUFMAN From a testing perspective, every newly diagnosed patient should have FISH evaluating for trisomies, evaluating for the 14-related translocations, including t(11;14) and 1q abnormalities. This should be the standard approach. An interesting question is whether we should do karyotyping. In data presented at the [American Society of Clinical Oncology], we showed that karyotyping patients who we thought were standard risk—because they didn’t have high-risk abnormalities—those who had conventional cytogenetic abnormalities have worse outcomes. The reality is that those abnormalities are in every patient, but our hypothesis is that if we can identify conventional cytogenetic abnormalities we can capture some patients that we wouldn’t have thought were high risk, but really are high risk. The standard remains measuring the amount of myeloma in the body, using the original biomarker, which is the monoclonal protein as measured by serum protein electrophoresis and urine protein electrophoresis. There’s an enormous amount of work involved in switching from relatively old technology of the electrophoresis and immunofixation to mass spectrometry.

Using flow cytometry to identify MRD [minimal residual disease], using next-generation sequencing to identify MRD, these things are ongoing, and as a community we’re just learning how to use these. I think the question becomes: When do we order the next-generation sequencing or whole-genome sequencing, so we can look for mutations?

From my perspective, the time to look is not necessarily at the newly diagnosed stage, but after initial, optimal therapy. In this situation, ordering [personalized approaches] like in MyDRUG may help us see whether we can identify that subgroup of patients that might have a targetable or an actual mutation. Outside of that study, we’ve started incorporating the whole-genome sequencing to look for recurrent mutations in that setting.

In terms of timing of testing, t(11;14) is important from the therapy standpoint. We know that many FISH abnormalities have contributed to the prognostication even if you may not necessarily differentiate on the initial therapy. Clinical trials and maybe clinical practice may be altered based on some of those prognostic markers, particularly the high-risk FISH abnormalities. It tells you about a choice between 2-drug maintenance vs 1-drug maintenance therapy and so forth. FISH testing at diagnosis is something that every patient with myeloma should absolutely have. We probably don’t need the more extensive and expensive molecular testing at the time of diagnosis, because we are anticipating a good median of 4 to 5 years without progression with modern therapies for newly diagnosed myeloma. Those tests are more likely to be useful at the time of relapse, when new abnormalities may emerge and the results may open opportunities for new therapeutic options, whether it’s part of clinical trial or outside. If patients have clinical behavior that seems to be quite different than one would anticipate from their baseline FISH findings and their relapse is early, those are times where we would want to do some of those next-generation sequencing type of testing. This is something that needs to be continually reassessed.

When I talk to colleagues and oncologists around the country, one of the questions is: If you do a test and you get the information, and you don’t act on that test, then what’s the use of it? The more we correlate these biomarkers with something to do, the more these barriers to testing are going to be broken down. ■

For a full list of references, see the article at OncLive.com
Antibody-Drug Conjugates (ADCs) have demonstrated substantial activity in patients with HER2-mutated non-small cell lung cancer (NSCLC), with fam-trastuzumab deruxtecan-nxki (Enhertu) showcasing the strongest response rate and progression-free survival (PFS) benefit to date. Progress continues to build for this patient population as efforts to better decipher HER2 signaling and more novel regimens show early signs of efficacy, according to Corey J. Langer, MD, FACP.

“Without question, trastuzumab deruxtecan holds the greatest promise…It is unclear whether this should move to the first line; I am on the fence myself,” Langer, who is director of thoracic oncology at University of Pennsylvania Abramson Cancer Center in Philadelphia, said in a presentation at the 23rd Annual International Lung Cancer Congress®. “We need more data on emerging agents, including mobocertinib [Exkivity], and certainly, we need to balance toxicity against efficacy.”

HER2 is overexpressed in 59% of NSCLC cases but HER2 mutations are rare, occurring in 3% of adenocarcinomas, mostly in the form of exon 20 in-frame insertions. “Phenotypically, these patients look very similar to EGFR- and ALK-mutated NSCLC: mostly never smokers and worse survival. …and certain of the other mutation-driven tumors,” Langer said. Langer is also a professor of medicine at the Hospital of the University of Pennsylvania.

Data leveraging the tumor-profiling multiplex panel MSK-IMPACT (Memorial Sloan Kettering integrated mutation profiling of actionable cancer targets) between 2014 and 2022 showed that 409 of 7993 patients harbored a HER2 aberration. Eight percent of patients with mutations had amplification, and 20% with amplifications had mutations.

Data from a study that examined overall survival (OS) from date of diagnosis in HER2-, EGFR-, and KRAS-mutated lung cancers showed that in the era before the introduction of ADCs, “outcomes for [patients] with HER2 mutations are not much different from KRAS mutations but certainly worse compared with EGFR mutations,” Langer said.

Most agents leveraged in NSCLC have been adopted following demonstrative efficacy observed in metastatic breast cancer, including lapatinib (Tykerb), afatinib (Gilotrif), dacomitinib (Vizimpro), trastuzumab (Herceptin), pertuzumab (Perjeta), ado-trastuzumab emtansine (Kadcyla; T-DM1), and trastuzumab deruxtecan.

Exposing the Role of TKIs
Relatively low response rates with tyrosine kinase inhibitors (TKIs) have limited their role for patients with HER2-mutated NSCLC. For example, among 26 patients who received dacomitinib, the overall response rate (ORR) was 12% (95% CI, 2%-30%), according to data from a phase 2 trial (NCT00818441). In 4 patients with HER2-amplified disease, the ORR with the agent was 0% (95% CI, 0%-60%).

Findings from a retrospective study of afatinib showed that among 23 evaluable patients with stage IV or recurrent HER2-mutated lung cancer, the ORR was only 13% (95% CI, 4%-33%).

Langer noted that despite the historic inefficiency of TKIs, newer agents appear to yield better responses.

Data from a phase 2 trial (NCT03066206) showed that among 12 evaluable patients with HER2 exon 20–mutant NSCLC, poziotinib (NOV120101; HM781-36B) elicited an ORR of 50% (95% CI, 21.1%-78.9%). Additionally, the irreversible pan-HER TKI pyrotinib was found to elicit an ORR of 53.3% in a cohort of 15 patients with HER2-mutant NSCLC, according to data from a phase 2 trial (NCT02535507).

“[However, these agents have] lots of toxicity, particularly poziotinib,” Langer said. Safety data showed that 56% of patients who received the agent on the trial experienced grade 3 or 4 treatment-related adverse effects (AEs). Sixty percent of patients experienced a toxicity that required a dose reduction, and 3% experienced an AE that resulted in discontinuation.

Entering the Modern Era of ADCs
ADCs are targeted agents with a monoclonal antibody component that identifies a specific antigen or receptor on the cell, delivering and releasing...
a cytotoxic drug linked to that antibody at the tumor site, Langer explained. Conceptually, these agents are designed to improve the efficacy of chemotherapy and reduce systemic exposure and toxicity.

“The ideal antibody will have high selectivity and affinity for the tumor-associated antigen and low immunogenicity. The selected antigen should have low prevalence on healthy tissues not shed into circulation, and the antibody should have a long-circulating half-life,” Langer said. “The linker that helps to pair the payload with the antibody should be stable in circulation and easily cleavable at the tumor site. The payload also must be effective enough to induce cell death with low toxicity. Ideally, there should be a short half-life and a high drug-antibody drug ratio.”

The 2 ADCs that have started to make their mark in the treatment paradigm are T-DM1 and trastuzumab deruxtecan, approved in August 2022.

Data from a phase 2 basket trial (NCT02675829) conducted at Memorial Sloan Kettering Cancer Center in New York, New York, showed that among 49 patients with ERBB2-amplified or -mutant lung cancer, T-DM1 elicited an ORR of 51%.7 In patients with HER2-mutant NSCLC (n = 18), the response was slightly lower, at 44% (95% CI, 22%-69%), with a median duration of response of approximately 4 months.8

The most common AEs reported with T-DM1 were elevated aspartate or alanine aminotransferase levels (grade 1, 39%; grade 2, 6%), thrombocytopenia (grade 1, 33%), fatigue (grade 1, 28%; grade 2, 6%), infusion reaction (grade 1, 11%; grade 2, 17%), and nausea (grade 1, 33%). Only 1 patient experienced a grade 3 effect, which was anemia, and no grade 4 or 5 toxicities were reported. 8

“Trastuzumab deruxtecan, first reported at [the American Society of Clinical Oncology Annual Meeting] 2 years ago in lung cancer, took us by storm,” Langer noted.

The novel ADC was evaluated at a dose of 6.4 mg/kg every 3 weeks in patients with nonsquamous NSCLC overexpressing HER2 or containing a HER2-activating mutation as part of the pivotal phase 2 DESTINY-Lung01 trial (NCT03505710).

Initial data from the cohort of patients with HER2 mutations (n = 42) showed that at a median follow-up of 8.0 months (range, 1.4-14.2), the agent elicited an ORR of 61.9% (95% CI, 45.6%-76.4%) per independent central review. The median PFS was 14.0 months (95% CI, 6.4-14.0), and the median OS was not reached (95% CI, 11.8–not evaluable).9

At a median follow-up of 13.1 months (range, 0.7-29.1), trastuzumab deruxtecan elicited a centrally confirmed objective response in 55% (95% CI, 44%-65%) of patients per independent central review assessment.10

Recent data published in the New England Journal of Medicine from DESTINY-Lung01 showed the continued benefit; however, Langer noted the longer follow-up demonstrated a decline in PFS.10 “There is nothing more sobering than additional phase 1 data, although the response rate is holding up for the most part,” Langer noted. “Remember, these are previously treated patients. The median number of prior [therapies received] was 2, and 95% of patients had prior platinum-based treatment. Two-thirds had prior immunotherapy.”

The median PFS with this additional follow-up was 8.2 months (95% CI, 6.0-11.9), and the median OS was 17.8 months (95% CI, 13.8-22.1).10

“[Although] the PFS has come down from 14 months to 8.2 months…that is still quite respectable,” Langer said.

The most common treatment-emergent AEs (TEAEs) experienced with trastuzumab deruxtecan were nausea and fatigue. Moreover, neutropenia and lung infections required dose interruptions and reductions.4 “Interstitial lung disease is a big class concern and certainly an AE of interest,” Langer said. “Eleven percent of patients had this, [although these effects] were mostly grade 2 and mostly responsive to steroids.”

TEAEs resulted in dose reductions for 38.1% of the 42 patients and dose interruptions in 59.5% of patients; these effects were drug related in 38.1% and 47.6% of patients, respectively. Moreover, 23.8% of patients experienced TEAEs that resulted in treatment discontinuation; 19.0% of these cases were related to the study drug.4
“[When looking at the] 2 ADCs side by side, clearly trastuzumab deruxtecan looks somewhat more active. That holds true when we compare this with other agents, including the TKIs that have been tested,” Langer said. “Response rates for the older drugs, for the most part, are below 50%, and [they also have] a shorter PFS and [OS].”

**Trastuzumab Deruxtecan: Which Line to Leverage?**

A study led by Mark G. Kris, MD, the William and Joy Ruane Chair in Thoracic Oncology at Memorial Sloan Kettering Cancer Center, examined whether oncologists would administer trastuzumab deruxtecan in the frontline or the second line.

Thirty-eight percent of attendings at the institution shared that they would administer the ADC in the frontline setting, followed by pemetrexed or cisplatin/carboplatin with or without pembrolizumab (Keytruda). Sixty-two percent shared they would use it in the second-line setting after chemotherapy with or without pembrolizumab.

“I was involved in a Research-to-Practice survey and the number for frontline [use] crept up a little bit, to 45%,” Langer said. “However, I still think the field is split on whether it should be utilized in the frontline [setting] or not. There is certainly interest in moving this [agent] earlier in treatment, potentially to the frontline setting.”

A phase 2 trial will evaluate neoadjuvant trastuzumab deruxtecan in patients with resectable stage II to III HER2-amplified and HER2-mutant lung cancer. To be eligible, patients must have an ECOG performance status of 0 or 1.

Study participants will receive the ADC at 5.4 mg/kg every 3 weeks for 2 cycles as neoadjuvant treatment. Following surgery and pathological response assessment, they will receive adjuvant treatment with standard-of-care platinum-based chemotherapy with or without immunotherapy per physician discretion and enter follow-up.

The primary end point of the trial is major pathological response, and secondary end points include pathologic complete response, ORR, nodal downstaging, event-free survival, disease-free survival, OS, and cell-free DNA clearance rate.

**CHECKPOINT INHIBITORS IN HER2-MUTATED NSCLC**

The role of PD-L1 and tumor mutational burden is another area of exploration in HER2-mutant lung cancers.

In a retrospective analysis, investigators evaluated historic trends in response of this patient population to immune checkpoint blockade.11 They identified 122 patients with HER2 mutations; 87 were identified through PD-L1 immunohistochemistry and 84 through next-generation sequencing.

Among 26 identified patients who received treatment, the ORR was 12% (95% CI, 3%-30%), with 3 patients reporting a partial response; 8 patients had stable disease, and 15 patients experienced disease progression. Notably, all responders had a PD-L1 expression of 50% or higher and/or a high tumor mutational burden.

The addition of chemotherapy to immune checkpoint blockade was also examined in patients with HER2-mutated NSCLC.12 Twenty-seven patients received this in the first-line setting. In treatment-naive patients who received chemotherapy, the ORR was 52%, the median PFS was 6 months, and the 1-year OS rate was 88%. “You see a short median PFS, even with the addition of chemotherapy,” Langer noted.

**REFERENCES**

1. Langer C. HER2 Tx in advanced NSCLC: from TKIs to ADCs. Presented at: 23rd Annual International Lung Cancer Congress®; July 28-30, 2022; Huntington Beach, CA.

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Value of Biomarkers for Immunotherapy in Advanced NSCLC Continues to Evolve

by KYLE DOHERTY

TRADITIONAL PREDICTIVE BIOMARKERS

for the efficacy of perioperative immunotherapy for patients with advanced non–small cell lung cancer (NSCLC), such as PD-L1 expression, still hold value but newer biomarker candidates such as minimal residual disease (MRD) are starting to make an impact, according to Solange Peters, MD, PhD. Peters provided an overview of immunotherapy biomarkers in a presentation during the 23rd Annual International Lung Cancer Congress.1

PD-L1 AND OTHERS DISPLAY MIXED RESULTS

In the phase 3 IMpower010 trial (NCT02486718), investigators enrolled 1280 patients with stage IB-stage IIIA NSCLC following resection and adjuvant chemotherapy. Patients received four 21-day cycles of cisplatin-based chemotherapy, plus pemetrexed, docetaxel, gemcitabine, or vinorelbine. Of the enrolled patients, 1005 were randomly assigned to receive either the anti–PD-L1 agent atezolizumab (Tecentriq) or best supportive care.2

In a subgroup analysis of disease-free survival (DFS) by PD-L1 status, investigators found that patients with high and intermediate PD-L1 levels derived greater benefit from treatment with atezolizumab compared with those with lower levels. The median DFS strongly favored the atezolizumab arm among the 229 patients with PD-L1 expression in at least 50% of tumor cells (HR, 0.43; 95% CI, 0.27-0.68).

Patients with PD-L1 expression in 1% to 49% of tumor cells (n = 247) also experienced a moderate benefit from treatment with atezolizumab compared with best supportive care (HR, 0.77-1.67). Similarly, patients who were current smokers (n = 139) did not experience a significant difference in DFS benefit between the 2 arms (HR, 1.01; 95% CI, 0.58-1.75). Median DFS did favor the atezolizumab arm among patients who were previous smokers (HR, 0.62; 95% CI, 0.47-0.81). “Remember that smoking history is not reliable in most medical charts,” Peters noted. “It has not been stratified for smoking history. You can have onco gene addiction in current smokers, and you have a very wide confidence interval. So, I do not think it has to be used as a biomarker.”

In terms of chemotherapy regimen, patients treated with docetaxel (n = 152) and vinorelbine (n = 303) both derived a DFS benefit from atezolizumab treatment (HR, 0.74; 95% CI, 0.45-1.23; and HR, 0.63; 95% CI, 0.43-0.91, respectively). However, neither gemcitabine (n = 165) nor pemetrexed (n = 385) favored atezolizumab in terms of DFS (HR, 1.03; 95% CI, 0.62-1.70; and HR, 0.91; 95% CI, 0.67-1.24, respectively).

“Is there any reason why gemcitabine will not be a good component to be given with immunotherapy?” Peters asked. “We have some data in advanced disease, but remember it is sequential. It just does not make sense to me; I think it is just a surrogate biomarker of other selection process for gemcitabine.”

The phase 3 KEYNOTE-091 trial (NCT02504372) enrolled patients with completely resected stage IB, II, or IIIA NSCLC and randomly assigned them to receive either the anti–PD-1 antibody pembrolizumab (Keytruda) or placebo. Peters focused on the biomarker potential of disease stage, treatment with adjuvant chemotherapy, and finished by again reviewing PD-L1 (TABLE).3

Results from a subgroup analysis showed that patients across disease stages derived a DFS benefit with pembrolizumab: stage IB (HR, 0.76; 95% CI, 0.43-1.37), stage II (HR, 0.70; 95% CI, 0.55-0.91), and stage IIIA (HR, 0.92; 95% CI, 0.69-1.24). However, she noted that these results do not make disease stage a sensible stratification tool because it is contrary to other data sets.

Additionally, patients who received adjuvant chemotherapy also benefited from treatment with pembrolizumab in terms of DFS (HR, 0.73; 95% CI, 0.60-0.89). Patients who did not receive adjuvant chemotherapy did not favor the pembrolizumab arm in terms of DFS (HR, 1.25; 95% CI, 0.76-2.05).

TABLE. DFS With Pembrolizumab vs Placebo in the KEYNOTE-091 Trial

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total number of patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1177</td>
<td>0.76 (0.63-0.91)</td>
</tr>
<tr>
<td>Stage IB</td>
<td>169</td>
<td>0.76 (0.43-1.37)</td>
</tr>
<tr>
<td>Stage II</td>
<td>667</td>
<td>0.70 (0.55-0.91)</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>339</td>
<td>0.92 (0.69-1.24)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>1010</td>
<td>0.73 (0.60-0.89)</td>
</tr>
<tr>
<td>No adjuvant chemotherapy</td>
<td>167</td>
<td>1.25 (0.76-2.05)</td>
</tr>
<tr>
<td>PD-L1 1PS &lt; 1%</td>
<td>465</td>
<td>0.78 (0.58-1.03)</td>
</tr>
<tr>
<td>PD-L1 1PS 1%-49%</td>
<td>379</td>
<td>0.67 (0.48-0.92)</td>
</tr>
<tr>
<td>PD-L1 1PS ≥ 50%</td>
<td>333</td>
<td>0.82 (0.57-1.18)</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; TPS, tumor proportion score.

“[I do not believe] that giving chemotherapy before immunotherapy can create a vaccine effect,” Peters said. “Does it mean that if you do not receive chemotherapy, you do not receive the vaccine [effect]? No. Patients who do not receive chemotherapy are a certain and defined subset of patients [for whom it will probably be very difficult to derive benefit from anything you could do afterward because of fragility, [adherence], or exposure to drugs. This is not a biomarker to me.” Results by PD-L1 tumor proportion score all demonstrated the benefit of pembrolizumab with the most pronounced among those with 1% to 49%: less than 1% (HR, 0.78; 95% CI, 0.58-1.03); 1% to 49% (HR, 0.67; 95% CI, 0.48-0.92); and at least 50% (HR, 0.82; 95% CI, 0.57-1.18). Peters noted that although the findings were properly stratified, the patients with lower PD-L1 levels benefiting more than those with high levels did not really make sense.

In the phase 3 CheckMate 816 trial (NCT02998528), patients with stage IB to IIIA resectable NSCLC were randomly assigned to nivolumab (Opdivo) plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. For this trial, Peters focused on PD-L1 status and chemotherapy type as potential biomarkers.4

In terms of event-free survival (EFS), patients with all levels of PD-L1 expression (< 1%; ≥ 1%; 1%-49%) and ≥ 50% derived a benefit with nivolumab plus chemotherapy. Patients with the highest level of PD-L1 experienced a 76% reduction in the risk of experiencing an EFS event and those with the lowest level reduced their risk by...
Pathology Expert Unpacks Future Role of MPR and pCR in Neoadjuvant NSCLC Treatment

by BRITTANY LOVELY

CLINICAL EFFICACY OF NEOADJUVANT treatment regimens for patients with non-small cell lung cancer (NSCLC) is increasingly being determined by major pathological response (MPR) and pathological complete response (pCR). However, these may be better leveraged as surrogates for survival outcomes than as markers of response to treatment. Neoadjuvant therapy is designed to resectable lung cancers with the hope of upstaging tumors or downstaging tumors to a surgically resectable stage, and the pCR rate is a key marker of success. However, a recent study from the IMpower010 trial showed that patients who received atezolizumab (PD-L1 inhibitor) plus chemotherapy had a higher pCR rate than those who received chemotherapy alone (HR, 0.61; 95% CI, 0.39-0.94). This finding suggests that the addition of immunotherapy to chemotherapy may improve the pCR rate and, therefore, the survival outcomes for patients with resectable lung cancer.

THE GROWING USE OF MPR AND pCR

Several phase 3 studies have used MPR or pCR as the primary end point for efficacy of neoadjuvant therapy for patients with metastatic NSCLC. For example, the dual primary end points of the phase 3 AEGEAN trial (NCT03800134) are pCR and event-free survival (EFS). The trial is evaluating the efficacy of neoadjuvant durvalumab (Imfinzi) plus standard-of-care platinum-based chemotherapy doublet vs standard of care alone. Recently, it was announced that the combination elicited a statistically significant and meaningful improvement in pCR as well as MPR. Analysis of data for EFS is ongoing and will be reported at an upcoming medical meeting.

In the phase 3 CheckMate 816 trial (NCT02998528), data published in the New England Journal of Medicine showed that patients with stage IB-IIIA resectable NSCLC who received nivolumab (Opdivo) plus platinum-based chemotherapy had a median EFS of 31.6 months (95% CI, 30.2-not reached) vs 20.8 months (95% CI, 14.0-26.7) with chemotherapy alone (HR, 0.63; 97.38% CI, 0.43-0.91; P = .005). In terms of pCR, 24% of patients who received the combination had a pCR vs 2.2% who received the standard of care (odds ratio, 13.94; 99% CI, 3.49-55.75; P < .001). MPR, CONTINUED ON PAGE 83
FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

BLENREP is the first and only BCMA-targeted ADC monotherapy. So you can offer your RRMM patients a different option.

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.

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

ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; RRMM=relapsed or refractory multiple myeloma.
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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

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

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4% of patients. Decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 20%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

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

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

ADVERSE REACTIONS
The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.14 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (21%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dose interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

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

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

Females and Males of Reproductive Potential: Based on findings in animal studies, BLENREP may impair fertility in females and males.

Geriatric Use: Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

Renal or Hepatic Impairment: The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)].

Notable requirements of the BLENREP REMS include the following:

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

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 15%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients.

Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dose and Administration (2.3) of full Prescribing Information].

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dose and Administration (2.3) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

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

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 1.3)].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2.

Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 99). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in ~3% of patients included pneumonia (2%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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

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

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

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

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

### Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Keratopathy</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>53</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>22</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>14</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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

Advising pregnant women of the potential risk to a fetus.

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

**Data**

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP: MMAF: disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation
Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].

• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:

• Patients must complete the enrollment form with their provider.

• Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia

• Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions

• Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].

• Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].

• Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

Infertility

• Advise males and females of reproductive potential that BLENREP may impair fertility [see Use in Specific Populations (8.3)].

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Produced in USA.
Other immunotherapy studies leveraging pCR and MPR as primary and/or secondary end points include the phase 3 IMpower030 trial (NCT03456063); the phase 3 KEYNOTE-071 trial (NCT03425643); and the phase 3 NeoAdAURA trial (NCT04351555). Wistuba noted that neoadjuvant approaches using targeted therapies are also underway and called attention to the Lung Cancer Mutation Consortium screening trial—LCRF LEADER (NCT04712877)—which aims to enroll 1000 patients with lung cancer who are candidates for neoadjuvant therapy to receive targeted agents for specific genetic mutations.1

“[As pathologists, we now must] be more careful on the assessment of these specimens,” Wistuba said.

ESTABLISHING DEFINITIONS FOR PATHOLOGISTS

Wistuba said that pathologists must also begin to integrate a new concept into routine practice, the tumor bed, which is a microscopic finding of a tumor and what was potentially tumor that has been modified by therapy. To establish the tumor bed, he noted that tumor grossing must include radiographic-pathologic correlation.

“We need to use more correlation with the images to better assess the area. We need to have a systematic [tissue] sample throughout the tumor and the tumor bed that sometimes can be confused with inflammatory processes that are going on adjacent to a tumor that is growing,” he explained. “We need to be able to identify residual tumor cells that are viable, [which is] sometimes not easy.”

Wistuba pointed out that pathologists must exercise caution when it comes to using terms as definitions may vary. “Viable tumor” should be used to describe the percentage of viable malignant cells in a specimen. “Tumor regression,” or “tumor bed,” should be used to describe the percentage of a tumor’s area that has responded to therapy. This includes necrosis, cavitation, and fibrosis, as well as areas with inflammatory or immune cell infiltration.

“Recently, we have fortunately seen pCR, [which] requires finding no viable malignant cells, but the sampling has to be complete of the specimen,” Wistuba said.

The definition for MPR—the presence of 10% or less of viable malignant cells—is based on observations from retrospective analyses from clinical trials that examined the efficacy of chemotherapy in the neoadjuvant setting. The definition is being used in trials for immunotherapy. “These retrospective studies showed that this percentage of 10% was critical to differentiate disease-free survival, and overall survival at 5 years in the chemotherapy-treated setting, [but] we haven’t seen any of these data in the monotherapy setting,” Wistuba said.

**FIGURE. Assessment Process for Resected Specimens for pCR and MPR**

**STEP 1** Measure gross maximum diameter

**STEP 2** Take hematoxylin and eosin-stained slides ≥ 1 section per greatest tumor diameter

**STEP 3** Measure percentage of viable cells in each slide

**STEP 4** Calculate the percentages to determine the mean residual viable tumor percentage

MPR, major pathological response; pCR, pathological complete response.

**STEPS FOR ASSESSING pCR AND MPR**

For NSCLC, Wistuba said there are 4 steps for assessing resected specimens for pCR and MPR. The first step is gross analysis that includes correlation with imaging. The second step includes taking stained slides of the specimen. “A good analysis of a specimen includes cavitation across it that needs to be reported carefully,” Wistuba said. “[For] appropriate sampling of the tumor, we use this principle: 3 cm or less, you put it all [on 1 slide]; more than 3 cm diameter, you can [create] 1 slide per cm.”

The third step is to measure the percentage of viable tumor cells in each slide and the fourth is to calculate the percentages to determine the mean residual viable tumor percentage (**FIGURE**). Some slides have a small piece of tissue [and] some have a larger piece of tissue, [and therefore there is some] suggestion to correct for the size of the specimens that you are analyzing. Then the percentage is based on the representation of tumors in a slide.

Wistuba noted that pathologists are using these protocols in the academic and institutional settings, but the challenge is to bring these to the community pathologists who are diagnosing lung cancer. He added that, unlike with breast or sarcoma samples, pathologists in lung cancer are not used to sampling an entire tumor and need more resources to make a diagnosis because they may be looking at 30 slides rather than 5.

“I think that the future of this is computational pathology using digital approaches,” Wistuba said. “There are several studies ongoing that are showing [digital approaches have] good correlation assessing MPR and pCR compared with observations of an experienced pathologist.”

One such study is the phase 2 LCMC3 trial (NCT02927301), which is evaluating atezolizumab (Tecentriq) as neoadjuvant therapy in NSCLC. Investigators evaluated computer vision machine learning and digital assessment of pCR using an artificial intelligence tool developed in accordance with consensus recommendations. The tool was trained to predict areas of tumor bed, viable tumor, stroma, and necrosis, and to label individual cells.

Cases were evaluated by local site pathologists as well as 3 central pathology experts using the definition of MPR of 10% or less of viable tumor cells. This analysis demonstrated that manual reporting was comparable to the digital assessment for pCR (98%) and MPR (91%). Further, digital pathological response demonstrated an “outstanding predictability” for manual assessment of MPR (area under the receiver operating characteristic, 0.973).

Wistuba concluded by noting that although the end points of MPR and pCR are important, improved outcomes for patients is what all clinicians are striving to achieve. He noted that these may represent appropriate end points for disease-free survival and overall survival and provide guidance for decision-making in the adjuvant setting.
EGFR TKI–Based Combinations Hold Potential to Reshape First-line Options in NSCLC

by CHRIS RYAN

LEVERAGING EGFR TYROSINE KINASE inhibitors (TKIs) as a backbone for combination therapies will be pivotal for expanding treatment options and delivering more personalized therapies in the first-line setting for patients with non–small cell lung cancer (NSCLC) harboring EGFR mutations, according to Marina Garassino, MD.1

Single-agent osimertinib (Tagrisso) remains the standard of care for patients with EGFR exon 19 and 21 mutations after data from clinical trials showed the EGFR TKI improved progression-free survival (PFS) and penetrated the central nervous system. However, combinations under investigation could further shift the treatment paradigm (TABLE). Garassino noted in a presentation at the 23rd Annual International Lung Cancer Congress® in Huntington Beach, California.

“We [must] tailor our treatments based on different types of mutations, the presence of comutations, and the clearance of DNA. There is a lot of work [being done] for this research,” said Garassino, a professor of medicine, Section of Hematology/Oncology, at The University of Chicago Department of Medicine in Illinois.

In April 2018, the FDA approved osimertinib as a first-line treatment for patients with NSCLC whose tumors harbor EGFR exon 19 deletions or EGFR exon 21 L858R mutations.2 The approval was based on data from the phase 3 FLAURA trial (NCT02996125) in which osimertinib elicited a median PFS of 18.9 months (95% CI, 15.2-21.4) vs 10.2 months (95% CI, 9.6-11.1) for standard TKI therapy with erlotinib (Tarceva) or gefitinib (Iressa; HR, 0.46; 95% CI, 0.37-0.57; P < .001).3

“There were no subgroups that did not benefit from treatment with osimertinib,” Garassino said. Additional data showed the median overall survival (OS) of osimertinib was 38.6 months (95% CI, 34.5-41.8) compared with 31.8 months (95% CI, 26.6-36.0) in the comparator arm (HR, 0.80; 95.0.5% CI, 0.64-1.00; P = .046).4

Other third-generation EGFR TKIs have displayed single-agent efficacy as a first-line treatment, Garassino explained. Aumolertinib was evaluated vs gefitinib in the phase 3 AENEAS trial (NCT03849768) for the treatment of patients with NSCLC harboring EGFR exon 19 deletions or EGFR exon 21 L858R mutations. Patients in the aumolertinib arm achieved a median PFS of 19.3 months (95% CI, 17.8-20.8) compared with 9.9 months (95% CI, 8.3-12.8) for those in the gefitinib arm (HR, 0.46; 95% CI, 0.36-0.60; log-rank P < .0001).1

“One question is: Can you use third-generation TKIs as [we use] osimertinib, or [do] we need to have head-to-head comparisons?” Garassino said, adding that this would apply to drugs developed in Asian countries as well.

EGFR TKI AND ANTI-VEGF COMBINATIONS

Preclinical data suggest dual blockade of the EGFR and VEGF pathways could be synergistic. Data have demonstrated improvements in PFS with the use of first-generation EGFR TKIs plus VEGF inhibitors compared with various single-agent treatments; however, these trials failed to demonstrate clinical benefits in OS, Garassino explained.

Investigators are awaiting OS data maturity from the phase 3 RELAY trial (NCT02414448). In the study osimertinib (Tagrisso), a first-generation EGFR TKI, was evaluated in combination with the VEGFR2 inhibitor ramucirumab (Cyramza) or placebo. Regarding the primary end point, the median PFS was 19.4 months (95% CI, 15.4-21.6) with the combination compared with 12.4 months (95% CI, 11.0-13.5) with erlotinib and placebo (HR, 0.591; 95% CI, 0.461-0.760; P < .0001).4 Other studies are exploring the combination of EGFR TKIs and VEGF inhibitors, including a phase 3 trial (NCT02824458) being conducted in China evaluating gefitinib with or without the VEGF2 inhibitor apatinib (Rivoceranib).2

COMBINING EGFR TKIS WITH CHEMOTHERAPY

Approximately 20% to 30% of patients with EGFR-mutated NSCLC do not survive to receive a second-line therapy, which has prompted investigators to examine the addition of chemotherapy to an EGFR TKI in the first-line setting. “With the chemotherapy we can potentially address cancer heterogeneity. We can kill the subclones that are resistant to the EGFR TKIs,” Garassino said.

The phase 3 NEJ009 trial (UMIN000006340) and a phase 3 clinical trial in India (CTR/2016/08/007149) both evaluated gefitinib alone vs gefitinib in combination with carboplatin and pemetrexed in patients with EGFR-mutated NSCLC.5,6

In NEJ009, the median OS with the combination was 52.2 months (95% CI, 44.0-not estimable) compared with 38.8 months (95% CI, 31.1-50.8) for gefitinib alone (HR, 0.695; 95% CI, 0.52-0.93). In data from the second study published by Noronha et al, the median OS was not reached (NR) with the combination vs 17 months with gefitinib alone (HR, 0.45; 95% CI, 0.31-0.65; P < .001).7

The phase 3 FLAURA2 trial (NCT04035486) will further evaluate the addition of chemotherapy for this patient population with osimertinib. Patients will be randomized to receive the EGFR TKI with or without pemetrexed and cisplatin or carboplatin following a safety run-in evaluating osimertinib in combination with the 2 chemotherapy regimens.8 “The future will be to address who

<p>| TABLE. Select Ongoing Trials With EGFR TKIs in NSCLC |
|---|---|---|</p>
<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial name (ClinicalTrials.gov identifier)</th>
<th>Intervention</th>
<th>Primary end point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>RELAY (NCT02414448)</td>
<td>Erlotinib plus ramucirumab vs erlotinib plus placebo</td>
<td>PFS</td>
</tr>
<tr>
<td>3</td>
<td>FLAURA2 (NCT04035486)</td>
<td>Osimertinib plus pemetrexed and cisplatin or carboplatin vs pemetrexed and cisplatin or carboplatin alone</td>
<td>PFS</td>
</tr>
<tr>
<td>2</td>
<td>NCT03292133</td>
<td>Gefitinib plus nazartinib</td>
<td>PFS</td>
</tr>
<tr>
<td>1/2</td>
<td>NCT03122717</td>
<td>Gefitinib plus osimertinib</td>
<td>Patients completing treatment</td>
</tr>
<tr>
<td>1*</td>
<td>CHRYSLAS (NCT02609776)</td>
<td>Dose-escalation: aminvamab monotherapy</td>
<td>DLT, AE, ORR, DOR</td>
</tr>
<tr>
<td>Combination: aminvamab plus lesthetic or amivantam plus carboplatin and pemetrexed</td>
<td>DLT, AE, ORR, DOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MARIPOSA (NCT04487080)</td>
<td>Aminvamab plus lesthetic or osimertinib plus lesthetic</td>
<td>PFS</td>
</tr>
</tbody>
</table>

AE, adverse effect; DLT, dose-limiting toxicity; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival.

*Recruiting.

1: 11.0-13.5 with erlotinib and placebo (HR, 0.591; 95% CI, 0.461-0.760; P < .0001). Other studies are exploring the combination of EGFR TKIs and VEGF inhibitors, including a phase 3 trial (NCT02824458) being conducted in China evaluating gefitinib with or without the VEGFR2 inhibitor apatinib (Rivoceranib).2

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EXAMINING EGFR TKI COMBINATIONS

By combining first-generation and third-generation EGFR TKIs, clinicians could potentially exploit the different affinity of the 2 agent classes to address the unmet need for patients with C797S mutations—one of the most common acquired mechanisms of resistance to osimertinib, Garassino explained. She added that several trials are ongoing to assess this strategy, such as a phase 2 trial (NCT03292133), evaluating gefitinib plus nazaritinib (EGF816) in patients with newly diagnosed EGFR-mutated NSCLC.11

Additionally, the combination of osimertinib plus gefitinib is being investigated in multiple studies, including a phase 1/2 trial (NCT03122717). Findings from this single-arm trial showed that patients treated with the combination (n = 27) had an overall response rate (ORR) of 88.9% (95% CI, 71.9%-96.1%) with a disease control rate of 100%. Notably, all responders had a partial response.11

Amivantamab-vnjw (Rybrevant) plus lazertinib (Leclaza) demonstrated activity following resistance to a first-generation EGFR TKI in the phase 1 CHRYSLALIS trial (NCT02609776).12 Among 45 patients who received the combination, the ORR was 36% (95% CI, 22%-51%) with a median duration of response of 9.6 months (95% CI, 5.3- NR) and 69% of responders had a response lasting at least 6 months. The median PFS was 4.9 months (95% CI, 3.7-9.5). The combination of amivantamab/lazertinib is now being evaluated against the combination of osimertinib/lazertinib in the phase 3 MARIPOSA trial (NCT04487080).

"In the future we will have to decide whether we need a combination therapy or an EGFR TKI alone. There are many potential opportunities for research," Garassino said. She concluded by noting that investigators are looking at driver mutation status, co-occurring mutations, and early plasma clearance.

REFERENCES


8. Nakamura A, Inoue A, Morita S, et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). J Clin Oncol. 2018;36(suppl 15);9005. doi:10.1200/JCO.2018.36.15_suppl.9005


New Treatments Are Needed for EGFR Exon 20–Mutated NSCLC

Erminia Massarelli, MD, PhD, MS, discusses the unmet needs for patients with EGFR exon 20–mutated non–small cell lung cancer. One patient population in need of new classes of drugs are those with brain metastases as available agents, such as mobocertinib (Exkivity) and amivantamab-vnjw (Rybrevant) do not have activity in the central nervous system, nor do they penetrate the blood-brain barrier.
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