Progress on New Therapies Stirs Hope in SCLC

PEER EXCHANGE
Immunotherapy Drives First-line Systemic Treatment for Advanced HCC

EphrinB2 Emerges as Targetable Option in UROTHELIAL CARCINOMA

CLINICAL PERSPECTIVES
Maheswari Senthil, MD, FACS, Discusses Intraperitoneal Chemotherapy Technique in GASTRIC CARCINOMATOSIS

CONFERENCE HIGHLIGHTS
Expert Insights From the 21st Annual International Congress on the Future of BREAST CANCER®

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Exploring High-Intensity Focused Ultrasound as an Organ-Sparing Option for PROSTATE CANCER
By Thomas P. Frye, DO

OncLiveLive
Expert Insights Into Oncology Research and Technology
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OncologyLive
Bringing the Global Oncology Community Together
IN ER+/HER2- METASTATIC BREAST CANCER (mBC)

CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

Complex mechanisms of estrogen receptor (ER) signaling have been associated with tumor growth.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?**

\textsuperscript{HER2}human epidermal growth factor receptor 2.

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The treatment paradigm for patients with small cell lung cancer (SCLC) has seen limited growth beyond standard chemotherapies. However, effort to leverage disease variation have uncovered molecular drivers of SCLC subtypes that may be useful in developing targeted therapies, setting a promising future for the field according to investigators.
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 tafasitamab-cxix (MONJUVI) in combination with lenalidomide as a second-line or subsequent therapy option for DLBCL in patients who are not candidates for transplant.1

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.
SECURE RESPONSE IN SECOND LINE

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.

†Assessed by an Independent Review Committee.1,3

‡Kaplan-Meier estimates.1,3

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

*R The 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.

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**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%

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**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**

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**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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**Additional Information**

11808936
REACH FOR MONJUVI

MONJUVI is second-line targeted immunotherapy for adult patients with DLBCL who are ineligible for transplant\(^1\)

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 MonjuviHCP.com
For information about patient assistance, visit MyMISSIONSupport.com

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


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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 with supportive medication.

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

**Myelosuppression**

MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12%, and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 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 2.5% of the 81 patients. Monitor patients for signs and symptoms of infection and manage infections as appropriate.

**Embryo-Fetal Toxicity**

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

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

**ADVERSE REACTIONS**

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in other clinical trials of another drug and may not reflect the rates observed with MONJUVI.

**Investigations**

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

- Muscle spasms
- Pruritus
- Rash
- Skin and subcutaneous tissue disorders

**Blood and lymphatic system disorders**

- Anemia
- Neutropenia
- Thrombocytopenia
- Febrile neutropenia

**General disorders and administration site conditions**

- Fatigue
- Pyrexia
- Peripheral edema

**Gastrointestinal disorders**

- Diarrhea
- Constipation
- Abdominal pain
- Nausea
- Vomiting

**Respiratory, thoracic and mediastinal disorders**

- Cough
- Dyspnea

**Infections**

- Respiratory tract infection
- Urinary tract infection
- Pyrexia
- Nausea
- Cough
- Vomiting
- Fatigue
- Rash
- Pruritus

- *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
- *Investigations: weight decreased
- *Musculoskeletal and connective tissue disorders: arthralgia
- *Nervous system disorders: headache
- *Neoplasms benign, malignant and unspecified: basal cell carcinoma
- *Respiratory, thoracic and mediastinal disorders: nasal congestion
- *Skin and subcutaneous tissue disorders: erythema

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

**Table 3: Adverse Reactions (% in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND**

**Adverse Reaction**

<table>
<thead>
<tr>
<th>MONJUVI (N=81)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>24</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
</tr>
<tr>
<td>Infections</td>
<td>Respiratory tract infection</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>16</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>19</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>15</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>10</td>
</tr>
</tbody>
</table>
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</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 assays. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other tafasitamab products may be misleading.

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

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

**Clinical Considerations**

**Fetotoxic/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. Refer administering live vaccines to neonates and infants exposed to tafasitamab-cxix in utero until a hematology evaluation is completed.

**Data**

**Animal Data**

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

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

MONJUVI can cause fetal B-cell depletion when administered to a pregnant woman. There are no available data on MONJUVI use in pregnant women to evaluate for a drug-associated risk. Refer to the lenalidomide prescribing information for additional information.

**Pregnancy Testing**

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

**Contraception**

**Females**

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

**Males**

Refer to the lenalidomide prescribing information for recommendations.

**Pediatric Use**

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

**Geriatric Use**

Among 81 patients who received MONJUVI and lenalidomide in L-MIND, 72% were 65 years and older, while 38% were 75 years and older. Clinical studies of MONJUVI did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs compared to that of younger subjects. Patients 65 years and older had more serious adverse reactions (57%) than younger patients (35%).

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full Prescribing Information.
Hurdles in Progress Place a Spotlight on Advances in SCLC

IMMUNOTHERAPY INDICATIONS FOR PATIENTS with metastatic small cell lung cancer (SCLC) did not fare well in 2021. Confirmatory data needed to support the continued approval for nivolumab (Opdivo) and pembrolizumab (Keytruda), respectively, failed to demonstrate the clinical benefit of these agents in the second-line setting. Manufacturers voluntarily withdrew the indications ahead of the FDA Oncology Drug Advisory Committee meetings.¹ ²

The headlines paint a grim picture for the population of patients with SCLC, necessitating an increased focus on successes made in the field. Taofeek Owonikoko, MD, PhD, wants to ensure that education on new advances reaches his thoracic oncology colleagues. “Forty percent of patients with SCLC may not get any treatment at all. That reflects the belief by most of our nononcology colleagues in other specialties such as pulmonary and internal medicine that once you have a diagnosis of SCLC there’s no effective treatment, [the patient] shouldn’t even bother going through any treatment,” Owonikoko said in an OncLive Peer Exchange program. “...Maybe over time, with education with our peers and colleagues, we are going to be able to change that paradigm.”

Our cover story provides a look at the ongoing investigational efforts and updated data that make the inches of progress seem like miles for a typically hard-to-treat population. This includes one group of patients generating the most success: extensive-stage SCLC. Most recently, front-line chemoinmunotherapy leveraging pembrolizumab showed prolonged benefit with 3-year follow-up data from the 3 KEYNOTE-604 study (NCT03066778).

Advances in the second-line setting, however, remain elusive with the last approval in the space occurring in 2020. Data from study B-005 (NCT02454972) supported the accelerated approval of lurbinectedin (Zepzelca) with a response rate of 35% reported among 105 patients who experienced disease progression.³ Building on these data, investigators have initiated the phase 3 confirmatory trial, LAGOON (NCT05153239).

Innovative trial designs are also exploring the potential of dual inhibition with lurbinectedin and pembrolizumab in this setting. Preliminary data from 13 patients treated in the phase 1/2 LUPER study (NCT04358237) showed an overall response rate of 30.8% and the median duration of response was not reached.⁴

Programs such as the Peer Exchange Owonikoko participated in, provide opportunities to contextualize clinical updates such as these in a digestible format. Through case-study discussions, episodes feature experts in the field reviewing current treatment algorithms as well as providing commentary on the latest data anticipated to effect clinical decision-making.

For updates regarding first- and second-line treatment algorithms for patients with SCLC you can use in practice today, begin watching the 15-episode OncLive Peer Exchange® "The Evolving Treatment Landscape of Small Cell Lung Cancer" at bit.ly/3ARGwVP.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®

REFERENCES
From the Editor

Benchmarks in Clinical Trial Design Require Closer Examination by Oncologists

by MAURIE MARKMAN, MD

DEVELOPMENT, INTERPRETATION, AND REPORTING of results from clinical trials in peer-reviewed literature form the basis of innovation in modern cancer medicine. In the hierarchy of such trials, the randomized phase 3 study, in which an experimental strategy is compared with a control arm, is supreme.

In most oncology settings the control arm is considered the standard-of-care option for the patient population at the time of trial initiation. Depending on the overall intent of the trial protocol, selection of the control arm may be determined by the study investigators, a sponsor (eg, pharmaceutical or device manufacturer) or a regulatory agency (eg, FDA).

In recent years there has been discussion in oncology literature regarding multiple aspects of randomized trials in cancer medicine. Topics often center on appropriate study end points required to achieve approval for commercial sale and the adequacy of subpopulation representation. A particularly vexing issue for some has been the role of so-called surrogate end points, such as progression-free survival (PFS) in obtaining regulatory approval vs other objective measures that may independently define clinical benefit.

However, less discussion surrounds the initial selection of appropriate study control arms. It is critical to appreciate that the results of most randomized trials in the oncology sphere are not available for at least several years following study initiation. As a result, it is possible that the control arm of a particular study will no longer be considered the standard of care when results become available to the oncology community. This outcome may occur if a presentation of study results during the interval following study activation reveal an alternative experimental strategy to be meaningfully superior to the standard-of-care regimen.

This issue once might have been far more theoretical than a reality because major changes to standards of care occurred infrequently. Consider, for example, primary therapy in advanced epithelial ovarian cancer, where use of a platinum agent (ie, cisplatin or carboplatin) plus a taxane (generally paclitaxel) was the undisputed standard of care for decades. Then, data became available regarding the favorable effect of bevacizumab (Avastin) on clinical outcomes. These findings resulted in regulatory approval adding this third antineoplastic agent to the dual cytotoxic drug strategy.

With regulatory approval of the 3-drug combination in the primary chemotherapeutic treatment of advanced ovarian cancer, the question is whether this regimen should be the required standard-of-care control arm in future studies in this clinical setting, or simply an option to be considered. If a phase 3 trial conducted for regulatory approval of a novel agent reveals an improvement in PFS compared with a control arm not containing bevacizumab, how should the results of this study be interpreted by the FDA, practicing oncologists, and patients with ovarian cancer requiring therapy in this clinical setting?

This thought experiment is not unique to ovarian cancer. In a recent commentary on randomized trials designed to examine new agents in the management of metastatic castration-resistant prostate cancer, Van Wambeke et al highlighted several clinical trials with clinically questionable control arms. In one case the control arm was stated to be physician’s choice but was limited to 1 of 2 antihormonal agents. These agents were selected based on the regimen the individual’s cancer had progressed on before entry into the study. In addition, a substantial percentage of patients eligible for enrollment had not received drugs known to be active in the clinical setting being examined.

This experience highlights a serious concern in trial development: protocols are not directly comparing novel strategies with relevant standard of cares. Further, trials are enrolling patients who have either not received the standard of care or have progressed following standard of care the setting being examined.

Unfortunately, the impressively rapid establishment of multiple pharmaceutical agents (with differing mechanisms of activity) approved by regulatory agencies in several clinical settings make it increasingly difficult to ensure that the trial-based populations objectively and appropriately represent a population for demonstrating a new drug’s effectiveness.

One strategy for circumventing this issue is to only permit patients entry into a trial if they have previously received...
From the Editor

all approved agents/drug classes in the clinical setting being examined. It is reasonable to suggest this is approach when a patient has previously received and progressed, failed to respond, or responded and then quickly progressed following standard-of-care therapy. For example, in ovarian cancer, this could include a patient with documented disease progression 3 months following initiation of primary platinum-based therapy. However, what if a patient with ovarian cancer treated with a first-line platinum-based regimen initially responds to therapy but has disease recurrence 6, 12, or 24 months following completion of the treatment program? Do they fit the definition of prior exposure to a platinum agent? The FDA has considered such patients to fall into 2 different regulatory categories, defined as follows:

- **Platinum resistant**: patients with no response, initial progression, or response followed by disease progression within 6 months of completing primary chemotherapy.

- **Platinum sensitive**: patients with response and progression more than 6 months after completion of primary chemotherapy. What about patients who have been treated with the standard-of-care cytotoxic chemotherapy regimen plus bevacizumab, followed by single-agent maintenance bevacizumab? Would it be fair to conclude that documented disease recurrence 12 months after completion of maintenance bevacizumab implies resistance to this antiangiogenic agent? Would a clinical trial examining a novel agent compared with a standard-of-care regimen not need to include bevacizumab?

Such a conclusion would be inappropriate because data from randomized trials have revealed that the administration of bevacizumab (plus chemotherapy) in certain ovarian cancer populations that previously received bevacizumab (plus standard-of-care cytotoxic regimen) can experience a superior outcome compared with chemotherapy alone. Therefore, if bevacizumab is not included in the control arm with the standard-of-care cytotoxic regimen, how does one know whether an outcome favoring the experimental agent is better in both efficacy and toxicity?

There are no easy answers to the questions posed in this commentary. These are factors to acknowledge and that should encourage open discussions between patients and oncologists about what data from randomized trials and regulatory approvals realistically provide in helping to select optimal therapy.

**REFERENCES**


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**ADVANCING PRECISION CARE THROUGH BIOMARKER-DRIVEN THERAPY:**

**CEACAM5 as a Therapeutic Target in NSCLC**

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Head, Medical Oncology Service
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INSIDE THE PRACTICE®
Integrative Oncology Approaches May Optimize Treatment Outcomes

Integrative oncology, the blending of complementary medicine with standard of care, has been a key focus for Kirsten West, ND, LAc, FABNO, who supports patients with cancer treated at the Riordan Clinic. West notes that patients are not as forthcoming with the supplements they are taking with their primary providers. She adds that open discussions across multidisciplinary teams will foster trust with the patient. West cites several trials exploring integrative approaches to care, including an exploratory phase 2 study of the benefits of mistletoe as an immune modulator for patients with solid tumors.

TO WATCH, VISIT bit.ly/3Q0ldXK.

MEDICAL WORLD NEWS DEEP DIVE®
Investigator Seeks to Uncover a Predicative Genome for Immunotherapy

Through an analysis of existing data from published cohorts, Neville Sanjana, PhD, discusses how his work at NYU Langone Health may help determine if exome sequencing can predict which patients would respond well to immunotherapy. Sanjana is looking at whether the number of tumor mutations or where the mutations in genes occur can serve as prognostic markers. He is using a 2-stage approach, nominating genes that appear mutated more often than expected and testing them for response. Sanjana notes that this research may also help to identify candidates better suited for combination therapy.

TO WATCH, VISIT bit.ly/3KB6rFQ.

AFTER HOURS™
A Vintage Collection Brings Character to Sciences

Perry N. Halkitis, PhD, MS, MPH, dean of Rutgers School of Public Health, has spent approximately 25 years of his career working as an epidemiologist to increase the knowledge base for HIV and other pathogens, most recently COVID-19. Although his research in the laboratory is intriguing, Halkitis sought to put “a face to the science” in his interview with After Hours, discussing his collection of vintage lunch boxes. He started collecting lunch boxes at aged 7 years, and his collection includes metal containers showcasing Star Wars and every member of the Justice League.

TO WATCH, VISIT bit.ly/3pWdoHZ.

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Beti-cel for β-thalassemia Requiring Transfusions Gains Approval

Betibeglogene autotemcel (beti-cel; Zynteglo) was approved by the FDA for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

Beti-cel is given in a single dose as a customized one-time gene therapy treatment in which a patient’s bone marrow stem cells are engineered to produce functional β-globin. It is the first gene therapy to be approved for this patient population.

Data from the phase 3 studies Northstar-2 (NCT02906202) and Northstar-3 (NCT03207009), along with findings from the long-term follow-up study LTF-303 (NCT02633943), supported the approval.

At a median follow-up of 24.3 months (range, 13.0-27.5) and 23 months (range, 4.1-26.8) in Northstar-2 (n = 23) and Northstar-3 (n = 18), respectively, 89% of all evaluable patients achieved transfusion independence for a median duration of 25 months (range, 12.5-38.5). A 2-year follow-up in the LTF-303 study showed 25 of 29 (86%) patients treated in the phase 3 studies achieved transfusion independence. The most common toxicities associated with the therapy were reduced platelet and other blood cell levels.

To read more, visit bit.ly/3PLX4E8.

Capmatinib Solidifies Role for NSCLC With MET Exon 14 Skipping Mutation

The FDA granted regular approval to capmatinib (Tabrecta), which was given accelerated approval on May 6, 2020, for adult patients with metastatic non-small cell lung cancer (NSCLC) with tumors having a mutation leading to a MET exon 14 skipping.

Additional data from the phase 2 GEOMETRY Mono-1 trial (NCT02414139) including 63 patients and 22 more months of follow-up supported the continued approval of the agent. Patients were required to have at least 1 measurable lesion and EGFR wild-type and ALK-negative status.

Treatment-naïve patients (n = 60) had an overall response rate of 68% (95% CI, 55%-80%), with a duration of response of 16.6 months (95% CI, 8.4-22.1). There was a complete response rate of 5% and a partial response rate of 63%. Previously treated patients (n = 100) had an overall response rate of 44% (95% CI, 34%-54%), with a duration of response of 9.7 months (95% CI, 5.6-13.0). All responses were partial responses.

To read more, visit bit.ly/38eruij.

FDA Grants Priority Review to Olaparib Treatment Regimen for mCRPC

The supplemental new drug application for the use of olaparib (Lynparza) in combination with abiraterone acetate (Zytiga) and prednisone or prednisolone to treat adult patients with metastatic castration-resistant prostate cancer has been granted priority review by the FDA. The agency is expected to make a decision in the fourth quarter of 2022.

The phase 3 PROpel trial (NCT03732820) findings supported the application. The trial enrolled patients with histologically or cytologically confirmed prostate adenocarcinoma who had at least 1 documented metastatic lesion.

Olaparib plus abiraterone acetate and prednisone or prednisolone was given to 399 patients and resulted in a significantly prolonged median imaging-based progression-free survival of 24.8 months vs 16.6 months for 397 patients who received placebo plus abiraterone acetate and prednisone or prednisolone (HR, 0.66; 95% CI, 0.54-0.81; P < .001). The overall survival data were immature at the time of the primary analysis.

Patients in the olaparib combination arm (n = 161) with measurable disease at baseline had an objective response rate of 40.3% compared with 48.1% in the placebo arm (n = 160) (odds ratio, 1.60; 95% CI, 1.02-2.53).

To read more, visit bit.ly/3wYAR5G.

NGS Companion Diagnostic Tacks on Indication for HER2-Mutated NSCLC

The FDA has approved the Oncomine Dx Target Test as a companion diagnostic to identify patients with non-small cell lung cancer (NSCLC) who harbor an activating HER2 mutation and may benefit from treatment with fam-trastuzumab deruxtecan-nxki (Enhertu).

The test is designed to simultaneously evaluate 23 genes associated with NSCLC and is a next-generation sequencing companion diagnostic first approved by the FDA in 2017. It is approved to identify 1 target for cholangiocarcinoma and 7 for NSCLC.

Trastuzumab deruxtecan was granted accelerated approval on August 11, 2022, for adult patients with unresectable or metastatic NSCLC with tumors having an activating HER2 mutation. Data from the phase 2 DESTINY-LUNG02 trial (NCT04644237) supported the approval; patients who experienced disease progression following previous systemic therapy (n = 52) had an overall response rate of 58% (95% CI, 43%-71%), with a median duration of response of 8.7 months (95% CI, 7.1- not estimable).

To read more, visit bit.ly/3Cvo33P.
Do you have a patient with relapsed/refractory adult B-cell acute lymphoblastic leukemia?

FELIX

We are conducting the single arm, open-label, multi-center phase 2 FELIX study (NCT04404660) to evaluate the investigational CD19 CAR T-cell product called AUTO1 (obecabtagene autoleucel or obe-cel) in patients with relapsed/refractory adult B-cell acute lymphoblastic leukemia. The primary objective of the study is to evaluate the safety and efficacy of AUTO1 given as a split dose on day 1 and on day 10. Following the initial dose of AUTO1, patients will be observed closely for at least 10 days in hospital. Patients will then be in follow-up until the end of the study. We are seeking assistance from referral centers and those physicians who treat adult B-ALL patients in regional community hematology/oncology clinics to help us identify qualified study participants.

clinicaltrials@autolus.com

www.autolus.com
FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU)

**Trastuzumab Deruxtecan Approval Provides New Path Forward for HER2-Low Breast Cancer**

*by MEGAN HOLLASCH*

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**THE APPROVAL OF FAM-TRASTUZUMAB** deruxtecan-nxki (Enhertu) for patients with HER2-low breast cancer has prompted conversations regarding the classification of HER2-mutant disease and the role that antibody-drug conjugates (ADCs) will play in the space.

On August 5, 2022, the FDA approved trastuzumab deruxtecan for adult patients with unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+ / in situ hybridization–negative) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.¹

The approval was supported by data from the phase 3 DESTINY-Breast04 trial (NCT03734029), in which trastuzumab deruxtecan resulted in a median progression-free survival (PFS) of 10.1 months (95% CI, 9.5-11.5) compared with 5.4 months (95% CI, 4.4-7.1) with chemotherapy (HR, 0.51; 95% CI, 0.40-0.64; P < .0001). Median overall survival (OS) was 23.9 months (95% CI, 20.8-24.8) vs 17.5 months (95% CI, 15.2-22.4), respectively (HR, 0.64; 95% CI, 0.40-0.86; P = .003).

"Trastuzumab deruxtecan is the first HER2-targeted therapy that has been active for [the] population of patients with HER2 low-level–expressing breast cancers, and not only is it active, [but] it’s much more active than what we normally treat these patients with," Shanu Modi, MD, said. "This is a drug that really improves and prolongs survival for patients with an advanced-stage, incurable cancer."

In an interview with OncologyLive®, Modi, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, discussed the significance of the approval.

**Please discuss the shift observed in HER2 classification.**

We normally classify breast cancers in a binary way: HER2 positive or HER2 negative. If cancer is HER2 positive, it means it has high levels of the HER2 protein [and], generally, a worse prognosis clinically. We have a lot of very active HER2-targeted therapies for HER2-positive breast cancer. Everything else we call HER2 negative, but that’s a real oversimplification because there are tumors within the HER2 negative population that also express the HER2 protein, just at lower levels.

It’s been a frustration that none of our current HER2-targeted therapies have been effective for those with cancers with low levels of that HER2 target.

**What have been the notable outcomes of the approval?**

I was impressed that the NCCN [National Comprehensive Cancer Network] guidelines committee moved very quickly [to add the agent to practice guidelines]. Trastuzumab deruxtecan [being regarded] as an option—as the only option for HER2-low breast cancer—almost within weeks of the data of being released [is significant].

Similarly, the FDA moved very quickly to review the data and approve trastuzumab deruxtecan. There is a lot of eagerness among clinicians to be able to offer this treatment to our patients. As you can see from the control arm in [DESTINY-Breast04], standard therapies are not very effective. It’s great that we now have access to this drug for a large group of our patients with metastatic disease.

**Please discuss the pivotal efficacy data from the DESTINY-Breast04 trial.**

DESTINY-Breast04 was a randomized study open to patients with HER2-low advanced-stage breast cancer. HER2 low was defined as tumors that had IHC 1+ or 2+ expression without gene amplification. To be eligible patients had to have received at least 1 line of chemotherapy but no more than 2 lines. Furthermore, patients who had hormone receptor–positive, HER2-low breast cancer also had to have received and have exhausted endocrine options.

This was a group of patients [who were] a little more heavily pretreated, and the study [randomly assigned] them to either standard of care—there was the option to use 4 or 5 different standard regular chemotherapy drugs, which they would normally [receive]—vs trastuzumab deruxtecan. The primary end point of the trial was PFS, and in this study, trastuzumab deruxtecan was able to double the duration of time that cancers were under control.

The median PFS period was [approximately] 5 months with standard chemotherapy and 10 months for the patients who [received] trastuzumab deruxtecan. Looking at OS, there was the same trend with standard chemotherapy. On average, patients had an OS of 17 months, and with trastuzumab deruxtecan, that improved to almost 2 years. These are clinically impactful results for a population of patients [for whom] we normally don’t see these kinds of improvements in survival when we introduce new agents in a later-line setting.

**What toxicities are associated with this agent?**

The toxicity is the important counterpoint to the efficacy of this drug, and we’ve been using trastuzumab deruxtecan in HER2-positive patients for a couple of years. We have a lot of experience with it.

The most common single toxicity is nausea, and thankfully it is a low-grade nausea. If you give your patients antinausea medications up front, you can control it. The other main category of the day-to-day toxicities is bone marrow suppression. This is something we’re familiar with managing as oncologists and [that] we can manage well with trastuzumab deruxtecan.

There is one important toxicity—and it’s important, not because it’s frequent or common, but because [of the] potential for it to be serious—and that’s lung toxicity. On average, we see lung toxicity reported with trastuzumab deruxtecan between 10% and 15% in different trials. For most patients, it’s a low-grade toxicity, you can stop therapy, it’s reversible, but there’s a small group of patients [in whom] it becomes a high-grade toxicity. We’ve seen fatalities from lung toxicity with trastuzumab deruxtecan; in [DESTINY-Breast04], it was less than 1% [at] 0.8%, so there were 3 reported cases of lung toxicity that were fatal.

It is a reminder for everyone, not only the physicians, but patients, that this is a toxicity that we must be aware of [and] the key to managing it is to...have a high threshold of suspicion and stop therapy if you suspect lung toxicity. [Detection] should launch an investigation into other causes, and if it really is trastuzumab deruxtecan–related lung toxicity, start steroids early.

**What do these data signal about the future of ADCs?**

These results from DESTINY-Breast04 are [about] much more than just breast cancer and this drug specifically. They are about progress in cancer therapy. [With] the technological evolution of an ADC, we’re now able to treat cancer so much more effectively [with] this strategy. The bystander effect [and] linker-payload technologies have evolved to a point that we’re able to see activity with a drug where we’ve never been able to before. I think this can apply to other cancers, and it can apply to other low-level targets; this is a real [step] forward in cancer therapy in general.

**REFERENCE**

**Drug Spotlight**

**BASELINE PATIENT CHARACTERISTICS:**

*All patients*

| Median age, years (range) | 57.5 (31.5-80.2) | 55.9 (28.4-80.5) |

**PHYSICIAN’S CHOICE OF CHEMOTHERAPY**

- **n = 373**
- **n = 184**

**Prior lines of therapy for metastatic disease**

| (range, 1-9) | 3 | (range, 1-8) | 3 |

**HER2-low status**

- **n = 371**
- **n = 172**

**REFERENCES**


**Mechanism of action**

- Trastuzumab deruxtecan is a humanized anti-HER2 IgG1 antibody-drug conjugate. The small molecule portion of the drug deruxtecan, is a topoisomerase 1 inhibitor attached to the antibody by a cleavable linker.

**How supplied**

- 100-mg single-dose vial of lyophilized powder for injection

**Dose**

- 5.4 mg/kg given as an intravenous infusion once every 3 weeks until disease progression or unacceptable toxicity

**Manufacturer:** Daiichi Sankyo, Inc

**PIVOTAL CLINICAL TRIAL**

DESTINY-Breast04 (NCT03734029) was a phase 3 trial evaluating trastuzumab deruxtecan vs physician’s choice of chemotherapy in adult patients with unresectable or metastatic HER2-low breast cancer. The trial included patients with hormone receptor–positive (primary efficacy population) and hormone receptor–negative disease.

**Efficacy results from the DESTINY-BREAST04 trial**

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**Confirmed ORR (95% CI)**

- Trastuzumab deruxtecan (n = 371)
- Chemotherapy (n = 172)

| CR | 3.6% | 0.6% | 3.5% | 1.1% |

| PR | 49.5% | 16.0% | 49.1% | 15.2% |

**Median DOR, months (95% CI)**

- Trastuzumab deruxtecan (n = 371)
- Chemotherapy (n = 172)

| 10.7 (8.5-13.7) | 6.8 (6.5-9.9) | 10.7 (8.5-13.2) | 6.8 (6.0-9.9) |

**Commonly reported AES in the DESTINY-BREAST04 trial**

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**Warnings and Precautions**

- Neutropenia
- Left ventricular dysfunction
- Embryo-fetal toxicity
- Interstitial lung disease/pneumonitis

**Box Warnings**

- Interstitial lung disease: Monitor for signs and symptoms of interstitial lung disease 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 interstitial lung disease/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.

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

**REFERENCES**

ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.¹⁻¹⁰

Until RYBREVA®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.¹¹

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVA® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVA®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range: 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVA® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVA® as recommended. Administer RYBREVA® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVA® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVA® based on severity.

Interstitial Lung Disease/Pneumonitis

RYBREVA® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVA®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVA® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVA® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions

RYBREVA® can cause rash (including dermatitis acneeform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVA®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVA® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVA®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVA®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
Results for tough-to-treat disease

3.7% of patients achieved a CR
36% of patients achieved a PR

*CHRYSLUS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBRENT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBRENT® was administered intravenously at 1050 mg for patients ≤80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.

^According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).

Based on Kaplan-Meier estimates.

The safety of RYBRENT® was evaluated in the CHRYSLUS* study (n=129)^:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity.
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%).
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphorus (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).
- IRRs occurred in 66% of patients treated with RYBRENT®, the majority of which may occur with the first infusion.

Based on the safety population, N=302.

The innovation you’ve been waiting for.

RYBRENT®

CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non–small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBRENT® based on severity.

Ocular Toxicity

RYBRENT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBRENT®. All events were Grade 1–2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBRENT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBRENT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBRENT®.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphorus (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Please see Brief Summary of full Prescribing Information for RYBRENT® on subsequent pages.


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RYVOREN™ (aminvamtam-vjm) injection, for intravenous use

Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYVOREN™ is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR mutation status (exon 20 insertion mutations). It is designed to deliver an FDA-approved test (see Dosage and Administration, 2.1) in Full Prescribing Information), whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response (see Clinical Studies, 14 in Full Prescribing Information). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS

Varicella-Zoster virus

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYVOREN™ can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, urticaria, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population (see Adverse Reactions), IRR occurred in 68% of patients treated with RYVOREN™. Among 65% experiencing IRR, 6% experienced severe IRR, while the incidence of IRR was 2.6% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively, 1.5% with subsequent infusions. Of the reported IRRs, 93% were Grade 1-2, 2.2% were Grade 3, and 4.6% were Grade 4.

Based on the median time to onset of infusion-related reactions (0.5 to 18 hours) after start of infusion, the incidence of infusion-related reactions due to RYVOREN™ was significantly less than that reported with docetaxel (31.9%).

The incidence of severe IRRs noted above was 2.2% (1/46) with RYVOREN™. Infusion-related reactions (IRR) may occur immediately after the completion of the infusion and may persist for weeks to months following completion of treatment.

Based on the safety population (see Adverse Reactions), IRR occurred in 17% of patients treated with RYVOREN™ (71/415). Patients with suspected IRR should be treated with IV fluids (e.g., saline, dextrose, and/or levodopa) and/or antihistamines.

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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 amivatantam-ab-vmiv products may not be meaningful.

In CHRYSELIS, 3 of the 28 (11%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA) tested positive for treatment-emergent anti-amivatantam-ab-vmiv antibodies (one at 27 days, one at 53 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryo-fetal death, malformations, and postnatal death in animals. (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivatantam-ab-vmiv on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGRF is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGRF signaling can prevent implantation, cause embryo-fetal death during various stages of gestation, and inhibit effects on placental development and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos or neonates of mice with disrupted EGRF signaling. Similarly, knock out of MET or its ligand HGF was embryonically lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in multiple organs. Human LEC1 is known to cross the placenta; therefore, amivatantam-ab-vmiv has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivatantam-ab-vmiv in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breastfed infants, advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

Advises females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

Pediatric Use

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

Geriatric Use

The 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 6% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions (see Warnings and Precautions).

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms (see Warnings and Precautions).

 Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UV/UVB sunscreens, and to wear protective clothing during treatment with RYBREVANT (see Warnings and Precautions). Advise patients to apply alcohol-free moisturizing cream to dry skin.

Ocular toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated (see Warnings and Precautions).

Paronychia

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia (see Adverse Reactions).

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, Use in Specific Populations).

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose (see Use in Specific Populations).

Product of Ireland

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During the past 15 years, breakthrough discoveries have revolutionized the treatment landscape for most patients with lung cancer, progress that has helped fuel an overall drop in cancer mortality. However, options remain limited for the subgroup of patients with small cell lung cancer (SCLC).

Against this backdrop, the treatment paradigm for patients with SCLC is evolving slowly beyond standard chemotherapy. Immune checkpoint inhibitor (ICI) combinations with chemotherapy have been incorporated into first-line treatment protocols for patients with extensive-stage SCLC (ES-SCLC) and the approval of lurbinectedin (Zepzelca), a novel form of chemotherapy, has expanded options for progressive disease.

Meanwhile, data for novel ICI combinations presented at recent medical conferences strengthen the case for such strategies in ES-SCLC, experts say. Additionally, efforts to study disease variation have uncovered molecular drivers of SCLC subtypes that may be useful in developing targeted therapies.

"Small cell lung cancer, despite being an uncommon disease, is one of the more aggressive cancers we know. It has a poor overall survival, and, despite making many survival-extending advances, both in targeted therapeutics as well as immunotherapy in non-small cell [lung cancer], we haven’t really done that well in the small cell [lung cancer] population," Joshua K. Sabari, MD, said during an OncLive® educational webinar in July 2022. Sabari is an assistant professor in the Department of Medicine at NYU Grossman School of Medicine in New York, New York.

"Clearly, more needs to be done. We need to understand the biology of this disease better, but as that research takes place, we need to follow best treatment practices as we now understand them," Sabari said.

That includes diagnosing patients and initiating therapy as early as possible during the course of disease, and closely monitoring responses for signs of recurrence and brain metastases, Sabari said.

Lung cancer experts who participated in a recent OncLive Peer Exchange® expressed excitement about an increasing number of clinical trials for patients with SCLC and the potential for research to yield novel, more effective therapies. However, they also noted that many patients are not benefiting from currently available options.

"When you look at the US population of patients diagnosed with small cell lung cancer, 40% of them may not get any treatment at all," Taofeek Owonikoko, MD, PhD, said. He is chief of the Division of Hematology/Oncology at the University of Pittsburgh School of Medicine in Pennsylvania and associate director for translational research at UPMC Hillman Cancer Center.

“That reflects the belief by most of our non-oncology colleagues in other specialties such as pulmonary and internal medicine that once you have a diagnosis of small cell there’s no effective treatment, [the patient] shouldn’t even bother going through any treatment," Owonikoko said.

"...Maybe over time, with education with our peers and colleagues, we are going to be able to change that paradigm."

The SCLC landscape

An estimated 236,740 patients are expected to receive a diagnosis of lung cancer in the United States in 2022, with approximately 85% of those cases classified as non–small cell lung cancer (NSCLC) and 15% as SCLC (Figure). Improvements in detection and treatment have helped drive down the mortality rates from lung cancer, significantly contributing to an overall decline in cancer mortality of 2% per year from 2015 through 2019, according to the American Cancer Society. However, most of the lung cancer gains are attributed to treatment advances for patients with NSCLC, because ICIs and molecularly targeted therapies have transformed the paradigm.

The discrepancy in outcomes for the 2 major subtypes is reflected in the 5-year relative
survival rate, which is 26% for patients with NSCLC and 7% for those with SCLC. With treatment, median overall survival (OS) for patients with SCLC ranges from 6 months to 24 months, depending on the extent of disease and stage at diagnosis.

Among patients with new SCLC diagnoses, approximately 12,000 are expected to present with limited-stage disease whereas about 23,000 will have extensive-stage disease. In limited-stage disease, the tumor is confined to 1 hemithorax, the mediastinum, or the supraclavicular nodes, such that the tumor fits within a single radiation field. Any disease that cannot be safely confined to a single radiation field is defined as extensive.

For patients with limited-stage SCLC, the goal of treatment is often curative through chemotherapy plus thoracic radiation therapy and, for some patients, surgical resection. For the majority of patients who are diagnosed with ES-SCLC, preferred systemic primary treatment involves combining a PD-L1 inhibitor, either atezolizumab (Tecentriq) or durvalumab (Imfinzi), with a chemotherapy doublet, according to National Comprehensive Cancer Network guidelines. Although the risk of relapse is high, more than 60% of patients consistently respond to cytotoxic therapies, including many patients with metastatic disease.

**FRONTLINE ICI APPROVALS**

Several studies have now demonstrated an improvement in overall survival with the addition of ICI therapy to chemotherapy in the frontline, although most of the gains are relatively modest (Table 11-14).

The FDA approved atezolizumab in combination with carboplatin and etoposide for the first-line treatment of adults with ES-SCLC in March 2019. A year later, the agency gave the go-ahead for durvalumab in combination with etoposide and either carboplatin or cisplatin as a first-line treatment for patients with ES-SCLC.

"If we look back on the past decade, the biggest advance is the addition of PD-L1 inhibitor therapy being added to the standard platinum etoposide regimen," Jared Weiss, MD, said during the OncLive Peer Exchange® program. "If you look at the evolution of frontline therapy before that, it was based on toxicity advantages and convenience advantages. These matter, but PD-L1 is our first survival advantage in a long time." Weiss is an associate professor of medicine-oncology at UNC Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

The FDA approved the atezolizumab regimen based on findings from the phase 3 IMpower133 trial (NCT02763579) for 403 patients who had received no prior chemotherapy for extensive-stage disease and had ECOG performance status 0 or 1. Median OS was 12.3 months (95% CI, 10.8-15.9) for patients receiving atezolizumab with chemotherapy and 10.3 months (95% CI, 9.3-11.3) for participants receiving placebo plus chemotherapy (HR, 0.70; 95% CI, 0.54-0.91; P = .0069). Median progression-free survival (PFS) was 5.2 months (95% CI, 4.4-5.6) with atezolizumab compared with 4.3 months (95% CI, 4.2-4.5) with placebo (HR, 0.77; 95% CI, 0.62-0.96; P = .0170). The objective response rate (ORR) was 60% with the atezolizumab regimen vs 64% with chemotherapy alone.

The combination of durvalumab plus chemotherapy gained approval based on OS results from 537 patients treated in the phase 3 CASPIAN trial (NCT03043872). The median OS was 13.0 months (95% CI, 11.5-14.8) in the durvalumab plus chemotherapy arm compared with 10.3 months (95% CI, 9.3-11.2) in the chemotherapy-alone arm (HR, 0.73; 95% CI, 0.59-0.91; P = .0047).

Investigator-assessed median PFS was 5.1 months (95% CI, 4.7-6.2) in the durvalumab arm and 5.4 months (95% CI, 4.8-6.2) in the chemotherapy-alone arm (HR, 0.78; 95% CI, 0.65-0.94). The ORR was 68% in the durvalumab group vs 58% with chemotherapy alone. Both ICI regimens maintained an OS benefit in updated findings reported in 2021. The median OS was 12.3 months (95% CI, 10.8-15.8) vs 10.3 months (95% CI, 9.3-11.3), respectively, for the atezolizumab-based and chemotherapy-alone regimens in IMpower133 (HR, 0.76; 95% CI, 0.60-0.95; P = .0154). At 18 months, the OS rate among patients who received atezolizumab was 34.0% compared with 21.0% for participants treated with chemotherapy alone.

Similarly, the median OS rate was 12.9 months (95% CI, 11.3-14.7) with durvalumab plus chemotherapy compared with 10.5 months (95% CI, 9.3-11.2) for chemotherapy alone in updated findings from CASPIAN (HR, 0.75; 95% CI, 0.62-0.91; P = .0032). The addition of durvalumab to chemotherapy resulted in a 32.0% OS rate at 18 months vs 24.8% with chemotherapy alone. (CASPIAN also included a third arm in which patients received durvalumab, the CTLA-4 inhibitor tremelimumab, and platinum-etoposide therapy, but that regimen did not significantly improve OS).

Although the addition of PD-L1 inhibitors to standard chemotherapy represents a step forward for the SCLC paradigm, many patients do not respond to these therapies, Charles M. Rudin, MD, PhD, noted during the OncLive Peer Exchange® program. "When they do work, they can be transformative," Rudin said. "There are patients who have durable responses even in extensive-stage disease so these [therapies] can really change a person’s fate. That’s something that was a long time coming and has clearly redefined our standard of care.”

Rudin is chief of the thoracic oncology service, codirector of the Druckenmiller Center for Lung Cancer Research, and the Sylvia Hassenzfeld Chair in Lung Cancer Research at Memorial Sloan Kettering Cancer Center in New York, New York. He is a leading investigator into the use of ICIs in patients with SCLC.
In August 2022, Rudin and colleagues presented long-term follow-up results from the phase 3 KEYNOTE-604 study (NCT03066778) at the 2022 World Conference on Lung Cancer sponsored by the International Association for the Study of Lung Cancer. The study tested the first-line use of pembrolizumab (Keytruda), a PD-1 inhibitor, combined with a chemotherapy doublet vs chemotherapy alone for patients with stage IV SCLC with no prior systemic therapy or unstable brain metastases and an ECOG performance score of 0 or 1. The dual primary end points were PFS and OS.

In all, 453 patients were randomly assigned to receive pembrolizumab (n = 228) or placebo (n = 225) plus etoposide with carboplatin or cisplatin every 3 weeks for 4 cycles. These regimens were followed in the experimental arm by pembrolizumab monotherapy and by placebo in the control arm for up to 31 cycles with optional prophylactic cranial irradiation. However, approximately 15% of patients in the chemotherapy-alone group subsequently received ICi therapy.

In previously reported findings, there was a trend toward an OS improvement with the pembrolizumab-containing regimen, but the outcome did not meet a prespecified threshold for statistical significance (HR, 0.80; 95% CI, 0.64-0.98; P = .0164). In the updated data, the median OS in the intention-to-treat (ITT) population after approximately 3.5 years’ follow-up was 10.8 months (95% CI, 9.2-12.9) among patients who received pembrolizumab compared with 9.7 months (95% CI, 8.6-10.7) for chemotherapy alone (HR, 0.76; 95% CI, 0.63-0.93). The median PFS in the ITT population was 4.8 months (95% CI, 4.3-5.4) with pembrolizumab plus etoposide with platinum chemotherapy vs atezolizumab plus chemotherapy followed by MK-7684A or atezolizumab, respectively. Vistobolimab is a monoclonal antibody directed at the TIGIT immune checkpoint.

**FIRST-LINE PEMBROLIZUMAB**

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**INVESTIGATIONAL ICi APPROACHES**

In another study, Rudin and colleagues sought to determine whether the addition of tiragolumab, a TIGIT inhibitor, to atezolizumab plus chemotherapy would improve outcomes for patients with treatment-naive ES-SCLC. Investigators randomly assigned 490 patients to tiragolumab (n = 243) or placebo (n = 247) combined with atezolizumab, carboplatin, and etoposide in the phase 3 SKYSCRAPER-02 trial (NCT04256421).

The use of tiragolumab failed to improve OS and PFS in all patients who received treatment (HR, 1.02 and 1.08, respectively) and in the primary analysis set of participants without a presence or history of brain metastases at baseline (HR, 1.04 and 1.11), according to findings presented at the 2022 American Society of Clinical Oncology Annual Meeting in June (2022 ASCO). However, investigators noted that the median OS outcomes in the control arm of atezolizumab plus chemotherapy confirmed its place as a first-line standard of care. The median OS was 12.9 months (95% CI, 12.1-14.3) in the full analysis set and 13.6 months (95% CI, 12.3-15.2) in the primary analysis set.

As development of FDA-approved ICis continues for SCLC indications, the novel PD-1 inhibitor serplulimab (HLX10) has demonstrated an OS benefit in combination with chemotherapy as a frontline treatment for patients with ES-SCLC in research conducted in China and several other countries. Interim findings from the phase 3 ASTRUM-005 study (NCT04063163) were presented at the 2022 ASCO.

In the study, 585 patients were randomly assigned 2:1 to receive either serplulimab (n = 389) or placebo (n = 196) with carboplatin plus etoposide, followed by serplulimab monotherapy or placebo, respectively. Key eligibility criteria included no prior systemic therapy for ES-SCLC and an ECOG performance score of 0 or 1. After a median follow-up of 12.3 months, the median OS in the serplulimab group was 15.4 months (95% CI, 13.3-17.5) compared with 10.9 months (95% CI, 10.0-14.3) in the placebo arm (HR, 0.63; 95% CI, 0.49-0.82; P < .001). The median PFS was 5.7 months (95% CI, 5.5-6.9) with the serplulimab regimen vs 4.3 months (95% CI, 4.2-4.5) with placebo plus chemotherapy (HR, 0.48; 95% CI, 0.38-0.59). The ORR was 80.2% with serplulimab and 70.4% with chemotherapy alone.

In April 2022, the FDA granted orphan drug status for serplulimab as a treatment for SCLC, which qualifies the drug for certain financial incentives, according to Shanghai Henlius Biotech, Inc, the company developing the drug. In China, the National Medical Products Administration approved serplulimab for microsatellite instability-high solid tumors in March 2022 and is considering a new drug application for the agent in first-line ES-SCLC.

**TABLE. OS Benefit With First-Line ICi Regimens in SCLC**

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>ICI combination</th>
<th>Median OS (95% CI)</th>
<th>Chemotherapy</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impower133*</td>
<td>Atezolizumab + EC*</td>
<td>12.3 months (10.8-15.8)</td>
<td>Placebo + EC</td>
<td>10.3 months (9.3-11.3)</td>
</tr>
<tr>
<td>CASPIAN*</td>
<td>Durvalumab + EP*</td>
<td>12.9 months (11.3-14.7)</td>
<td>EP</td>
<td>10.5 months (9.3-11.2)</td>
</tr>
<tr>
<td>KEYNOTE-604</td>
<td>Pembrolizumab + EP</td>
<td>10.8 months (9.2-12.9)</td>
<td>Placebo + EP</td>
<td>9.7 months (8.6-10.7)</td>
</tr>
<tr>
<td>ASTRUM-005</td>
<td>Serplulimab + EC</td>
<td>15.4 months (13.3-NE)</td>
<td>Placebo + EC</td>
<td>10.9 months (10.0-14.3)</td>
</tr>
</tbody>
</table>

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**SECOND-LINE FAILURES AND ADVANCES**

Although ICi therapy is solidifying a place in the frontline treatment of ES-SCLC, its efficacy as monotherapy for progressive disease has faded. In 2018, the FDA granted an accelerated approval for nivolumab (Opdivo), a PD-1 inhibitor, as a second-line therapy for patients with metastatic SCLC whose disease progressed after treatment with platinum-based chemotherapy and at least 1 other line of therapy, based on response rates and DOR data from the phase 1/2 CheckMate-032 trial (NCT01928394). However,
Bristol Myers Squibb withdrew the indication in December 2020 after data from confirmatory studies failed to support a benefit.

A similar scenario unfolded with pembrolizumab, which also received an accelerated approval as a second-line therapy in patients with metastatic SCLC that progressed after prior chemotherapy in June 2019, based on tumor response rate and from cohort G of the phase 2 KEYNOTE-158 trial (NCT02628067) and cohort C1 of the phase 1 KEYNOTE-028 (NCT02054806) study. Merck withdrew the indication in March 2021 after findings from subsequent clinical trials did not confirm an OS improvement.

Meanwhile, lurbinectedin was introduced into the treatment landscape for second-line therapy in June 2020. Until then, the only FDA-approved option for second-line therapy for SCLC was topotecan (Hyocin), a topoisomerase I inhibitor that gained its initial indication in the malignancy in 1998.5,13,14

Lurbinectedin is an alkylating drug that binds to DNA, setting off a cascade of events that may disrupt DNA binding proteins and repair pathways, resulting in cell death. The agent also may affect the tumor microenvironment through several mechanisms that cause apoptosis of peripheral blood monocytes and tumor-associated macrophages, decrease expression of the inflammatory chemokines, and reduce tumor angiogenesis.14,16

The FDA granted an accelerated approval for lurbinectedin in adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy based on findings from the phase 2 PM1183-B-005-14 trial (Study B-005; NCT02454972).

Among 105 patients treated during the study, the investigator-assessed ORR was 35% (95% CI, 26%-45%) and the median DOR was 5.3 months (95% CI, 4.1-6.4). Outcomes were better for the cohort of 60 patients who had platinum-sensitive SCLC, defined as recurrence or progression 90 days or longer after the last dose of platinum-containing therapy. For these patients, the investigator-assessed ORR was 45% (95% CI, 32%-58%) and the median DOR was 6.2 months (95% CI, 3.5-7.3).15,16

In December 2021, investigators launched the confirmatory phase 3 LAGOON trial (NCT05153239), which was designed to establish the efficacy of lurbinectedin for full FDA approval. The trial, which has a target enrollment of approximately 700 patients, is randomly assigning participants to 1 of 3 arms: lurbinectedin monotherapy at 3.2 mg/m² intravenously (IV); lurbinectedin at 2.0 mg/m² IV plus irinotecan 75 mg/m² IV; investigator’s choice of topotecan at 2.3 mg/m² orally or 1.5 mg/m² IV, or irinotecan at 350 mg/m² IV. The primary end points are OS and PFS.17

THE SEARCH FOR MOLECULAR TARGETS

In NSCLC, the development of tyrosine kinase inhibitors has made treatment for the tumor type a prime example of molecularly targeted therapy.2 However, similar progress has proved elusive in SCLC. Nearly all cases of SCLC are associated with smoking and its mutational profile reflects the impact of tobacco carcinogens in driving disease. Whereas NSCLC is driven by activating oncogenic alterations, the development of SCLC involves the dual inactivation of the tumor suppressor genes TP53 and RB1.18

“Genetically, what we see across the board in patients with small cell lung cancer is inactivation or loss of TP53, a gene responsible for fixing other abnormalities. We also see loss of RB1 or retinoblastoma, and these 2 alterations are very difficult to target in patients with small cell lung cancer,” Sabari said. “Unlike EGFR mutations, for example, which we can act upon with tyrosine kinase inhibitors, there are no FDA-approved therapies for these alterations in small cell.”

Although genomic analysis is not yet used to develop prognoses or drive treatment, investigators have identified 4 distinct subtypes of SCLC based on differential levels of transcription factor expression: ASCL1 (SCLC-A subtype), POU2F3 (SCLC-P), NEUROD1 (SCLC-N), and YAP1 (SCLC-Y). The subtypes account for approximately 70%, 16%, 11%, and 2% of cases, respectively.19

In 2021, investigators identified an inflamed subtype (SCLC-I) characterized by low expression of ASCL1, NEUROD1, and POU2F3, according
to Carl M. Gay, MD, PhD, and colleagues at The University of Texas MD Anderson Cancer Center in Houston. An analysis of SCLC circulating tumor cells in xenograft models showed that the SCLC-L subtype is more likely to respond to ICI therapy whereas the other subtypes might respond to inhibitors targeting PARP, aurora kinases, or BCL-2.28

“Based on these separate classifications of small cell lung cancer, we’re starting to tease out potential subsets of patients who may benefit from specific therapies,” Sabari said. “More recently, there is a paper from Carl Gay’s group at MD Anderson that takes this to the next level to seek a more inflamed subtype of small cell lung cancer [in which] patients may benefit further from immunotherapy than others. Again, these subclassifications are not currently used in clinical practice, but they may help in the future with prognosis, treatment, and, more importantly, the development of clinical trials for specific subsets of patients.”

REFERENCES

Q What pending studies may make a difference in this space?

One important question of the present is how to manage the risk of brain metastases in SCLC, particularly in the early stage or limited stage. Older historical data have shown a survival benefit to doing prophylactic cranial irradiation as a way of heading off the development of symptomatic metastases. In the past, that has shown a survival benefit, but that is based on older data where we didn’t have as good staging as we do now, for example, with MRI scans. A question now is in a truly earlier stage with proper staging, is there a benefit to prophylactic cranial irradiation? Can it be optimized? That is being studied in an ongoing clinical trial, MAVERICK [SWOG 1827; NCT04155034].

Another emerging area that is still being defined with respect to the treatment of brain metastases—this is for extensive-stage SCLC that has involved the brain—is the role of stereotactic radiation as opposed to whole brain radiotherapy. Some very interesting data have emerged, somewhat counterintuitive to notions in the past, [showing] that stereotactic radiation may indeed be an effective treatment for brain metastases in SCLC. There is at least 1 ongoing randomized clinical trial including [patients with] both limited- and extensive-stage SCLC and treatment of brain metastases [NRG-CC009; NCT04804644].

Q What is important for your oncology colleagues to know about treating patients with SCLC?

One important [facet] is that the optimal use of radiation therapy, which is my specialty, is still actively evolving. In the care of patients with SCLC, just as with NSCLC, it is critical to have that input and feedback from radiation oncology and to have that multidisciplinary coordination. That is particularly important in the care of patients with SCLC, who tend to have more aggressive course of disease and who may have more baseline comorbidities.
Clinical Research Study: KN-4802

Now enrolling adult patients with FGFR2 and/or FGFR3 alterations with solid tumors

Study Synopsis

KN-4802 is a multi-center, open-label, two-part clinical trial sponsored by Kinnate Biopharma Inc. to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of KIN-3248, an irreversible, covalent, small molecule pan-FGFR inhibitor, in adults (18+) with advanced tumors harboring FGFR2 and/or FGFR3 gene alterations and known secondary FGFR resistance mutations.

The dose escalation portion (Part A) of the trial will determine the recommended dose and schedule of KIN-3248 for further evaluation in the expansion portion in participants with solid tumors harboring FGFR 2 and/or FGFR3 alterations.

The dose expansion portion (Part B) will evaluate the safety and efficacy of KIN-3248 at the recommended dose and schedule in participants with tumors harboring FGFR2 and/or FGFR3 gene alterations, including intrahepatic cholangiocarcinoma (ICC), urothelial cancer (UC), and other solid tumors.

The U.S. Food and Drug Administration (FDA) cleared the Investigational New Drug application for KIN-3248 in January 2022 and the trial was initiated in the first quarter of 2022. More information can be found at: ClinicalTrials.gov/ct2/show/NCT05242822
Immunotherapy Drives First-line Systemic Treatment for Advanced HCC

by BRITTANY LOVELY

EVIDENCE-BASED DECISIONS HAVE lever-aged the use of immunotherapy (IO) combination atezolizumab (Tecentriq) plus bevacizumab (Avastin) for patients who receive a diagnosis of hepatocellular carcinoma (HCC). Approved in 2020, the combination has become a category 1 recommendation in the National Comprehensive Cancer Network guidelines and set the standard for first-line treatment.1,2

However, decisions may vary for patients who present with unfavorable clinical profiles. This includes those at an elevated risk of bleeding, Child-Pugh status, or contraindications such as autoimmune disease.2 Other contenders in the armamentarium include alternate immunotherapy combinations and single-agent tyrosine kinase inhibitors (TKIs) may hold a role for select patients with advanced HCC, but clearer stratification factors and real-world data are needed to solidify their role in the treatment landscape.

“If a patient is a candidate for IO and does not have contraindications to VEGF therapy, they’re going to get atezolizumab/bevacizumab,” Anthony B. El-Khoueiry, MD, said in a recent OncLive Peer Exchange®. “If they’re not a candidate for combination—and that’s in the eye of the beholder to some extent, maybe liver function is weighing in—you can use single-agent sorafenib, or single-agent anti-PD-1/PD-L1, and if they have IO contraindications, they’re going to get a TKI. With the new regimens that come on board we’ll see the data and how positive or negative they are.”

El-Khoueiry and a panel of liver cancer experts held a case-based discussion centered on updates in the systemic treatment of patients with advanced HCC and the clinical factors that may influence decisions that diverge from the standard IO/IO approach.

THE STANDARD OF CARE IN ADVANCED HCC

To guide the discussion of first-line systemic treatment options, the case of a woman aged 63 years with chronic active hepatitis C infection was referenced (FIGURE). After starting antiviral therapy, she presented with elevations on liver function tests, which prompted a CT scan of the abdomen. Multifocal infiltrative liver lesions were observed in the right lobe with evidence of vascular invasion by the tumor and the patient received a diagnosis of HCC.

“This is a patient who has Child-Pugh A cirrhosis, has prototypical BCLC [Barcelona clinic liver cancer] staging with a tumor invading a large blood vessel,” Pierre Gholam, MD, said. “She does not appear to have any significant contraindications to the combination of atezolizumab and bevacizumab and based on the evidence that would be our go-to first-line model.”

Mark Yarchoan, MD, concurred adding, “This is the preferred first-line systemic regimen for individuals who are eligible for it.”

Yarchoan cited data from the phase 3 IMbrave 150 study (NCT03434379) in which the combination was evaluated against single-agent sorafenib (Nexavar).1,2 “This was a positive study regarding every end point that we care most about: overall survival [OS], progression-free survival [PFS], objective response rate [ORR], and even quality of life. You really need a reason not to use it in first line.”

Updated data from IMbrave 150, published in 2022, highlighted the prolonged clinically meaningful benefit with the combination in the first line (TABLE).2 Further, real-world data of the

**FIGURE. Case: Patient With Newly Diagnosed Advanced HCC**

<table>
<thead>
<tr>
<th>History</th>
<th>Medical history</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, age</td>
<td>Chronic active hepatitis C; recently started antiviral therapy</td>
<td>Elevated liver function tests</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Workup</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient imaging</td>
<td>CT of the abdomen showed multifocal infiltrative liver lesion on the right lobe enhancing tumor thrombus in the right lobe posterior portal vein bland-appearing thrombus at splenic confluence and superior mesenteric vein nodular surface liver</td>
</tr>
<tr>
<td>Patient laboratory work-up</td>
<td>Platelets 68,000</td>
</tr>
<tr>
<td></td>
<td>Bilirubin 1.3; albumin 3.7</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C virus RNA 1 million IU/L</td>
</tr>
</tbody>
</table>

| Patient diagnosis | HCC Child-Pugh A ECOG performance status 0 |

AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; HCC, hepatocellular carcinoma.
“EMERGING TREATMENT CONSIDERATIONS IN HEPATOCELLULAR CARCINOMA: AN EXPERT CASE-BASED DISCUSSION”

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regimen showed that the combination may be administered beyond the criteria of the IMbrave 150 study and support its role as an option for patients with liver impairment including Child-Pugh B status.4

Among 202 evaluable patients, 154 had Child-Pugh A classification and 48 had Child-Pugh B classification. The median OS for all-treated patients was 14.9 months (95% CI, 13.6-16.3) with a 6-month OS rate of 77% and a 12-month OS rate of 60%. When stratified by Child-Pugh classification the median OS for those with A classification was 16.8 months (95% CI, 14.1-23.9) vs 6.7 months (95% CI, 4.3-15.6) for those with B classification. The median PFS of the overall population was 6.8 months (95% CI, 5.2-8.5) and the was 7.6 months (95% CI, 6.2-8.9) for patients with Child-Pugh A and 3.4 months (95% CI, 2.6-4.2) for patients with Child-Pugh B classifications.

Responses, evaluated using RECIST 1.1 criteria, were comparable to the rates seen in IMbrave 150. In the overall population evaluable for response (n = 174), the objective response rate was 25% and was 26% and 21% in the Child-Pugh A (n = 140) and Child-Pugh B (n = 34) populations, respectively.4

Addressing the increased risk of bleeding, the investigators of the real-world analysis noted, “the proportion of patients who experienced bleeding events in our study was comparable between patients with Child-Pugh A and patients with Child-Pugh B, not diverging from rates observed in IMbrave150.”4

Moderator Tanios S. Bekaii-Saab, MD, asked for considerations that may deter from the use of the combination. “When combining these agents [there is concern] for risk of bleeding, primarily related to portal hypertension,” Gholam said. “I think one would be well-advised to assess portal hypertension risk in this patient with Child-Pugh A status. We can now do this to some extent noninvasively, although certainly the broader hepatology and medical oncology community has relied on endoscopy to assess for the presence of esophageal or gastric varices. The fact that cross-sectional imaging does not show splenomegaly, abdominal varices, or esophageal varices is reassuring [for this patient]. Depending on where the tumor is located, [liver elastography] may or may not be a good test because, remember, if you have a tumor, this could alter the stiffness of the liver and may give you erroneous information. But that is a possibility. There are other tests for assessment of fibrosis, but, in general, nothing points to limitations in our ability to initiate atezolizumab/bevacizumab. There’s no uncon-rolled hypertension and there doesn’t appear to be any underlying autoimmune disease that would be adversely affected by that combination.”4

In terms of considering other factors that may point clinicians to an alternative, those with nonviral HCC may benefit from treatment with the TKI lenvatinib (Lenvima).5 Data from a prospective study of patients with advanced HCC or intermediate HCC who were not eligible for locoregional therapies showed that those who received atezolizumab plus bevacizumab (n = 190) had inferior outcomes compared with lenvatinib (n = 569). Among all-treated patients, the median OS was 17.8 months (95% CI, 15.8-43.8) with the TKI vs 12.1 months (95% CI, 11.1-16.8) for patients treated with the combination (HR, 0.71; 95% CI, 0.50-1.06; P = .1028). An analysis of patients with nonalcoholic fatty liver disease (ANFLD)/nonalcoholic steatohepatitis (NASH) showed an OS advantage favoring single-agent TKI treatment. The median OS was 21.2 months (95% CI, 18.4-30.6) with lenvatinib (n = 254) vs 12.1 months (95% CI, 10.0-16.8) with the combination (n = 82; HR, 0.46; 95% CI, 0.25-0.88; P = .0181).5

“When sorafenib came out there was an impression that there was an enhanced response in patients who had viral hepatitis,” Gholam said. “In fact, there were studies, some of which I participated in, which showed that perhaps sorafenib has a weak antiviral activity, reduces hepatitis C viral load by perhaps a half log. This has continued as TKIs came to the forefront.”

Gholam pointed to a study from Heikenwälder et al in a paper published in Nature which analyzed outcomes with immunotherapy in patients with NASH.6 Investigators noted that unconventional activation of
CD8-positive/PDI-positive T cells drive carcinogenesis in the setting of fatty liver disease and, in turn, diminish response to IO therapy. “I think this issue is at the same time important and also poorly understood,” Gholam said. “Does that mean that I would make different treatment decisions if I had a patient in front of me who had NAFLD in terms of deciding what treatment option to give them? Within the parameters that outlined in the discussion, I would still choose the [atezolizumab/bevacizumab] option. But this is an important question to ask because fatty liver disease has now become the leading cause of liver disease worldwide. Hepatitis C is on the decline curable.”

ALTERNATIVE FIRST-LINE COMBINATIONS ARE UNDER EVALUATION HIMALAYA

Alternative combination strategies have been evaluated in the first-line setting vs single-agent TKIs; however there has been no movement to dethrone the approved IMbrave 150 regimen. Specifically, data from the phase 3 HIMALAYA trial (NCT03298451) have set the IO combination of durvalumab (Imfinzi) and tremelimumab on course as a viable option for this patient population. However, without an approval, it holds a on course as a viable option for this patient population.7

Investigators assessed a regimen known as STRIDE, which includes a single dose of tremelimumab (300 mg) plus durvalumab (1500 mg every 4 weeks). “HIMALAYA was intended to examine the concept of IO/IO combinations looking at the combination of anti-PD-L1 durvalumab with anti-CTL4 tremelimumab,” El-Khoueiry said. “The way tremelimumab was given in this study is with 1 loading dose based on preclinical evidence that the dose could alter the immune microenvironment, and then [treatment could] continue with durvalumab as a single agent. This loading dose of tremelimumab was a higher dose than normally used at 300 mg compared with the traditional dose of 75 mg.”

Patients were randomly assigned to STRIDE (n = 393), single-agent durvalumab (n = 389), or sorafenib (n = 389). Median OS was 16.43 months (95% CI, 14.16-19.58) with STRIDE vs 13.77 months (95% CI, 12.25-16.13) with sorafenib (HR, 0.78; 96.02% CI, 0.65-0.93; P = .0035). The HR for OS for durvalumab vs sorafenib alone was noninferior (HR, 0.86; 95.67% CI, 0.73-1.03). The OS rates at 36 months were 30.7%, 24.7%, and 20.2%, respectively.

“Some of the strengths of this trial are that it’s really the largest randomized phase 3 study in first-line HCC,” El-Khoueiry said. “It is very mature with long follow-up. For the first time we’re seeing 36-month OS rates. Certainly, at 36 months, the combination still was superior to sorafenib, so those curves diverge and stayed separate for a long time.”

Yarchoan noted that cross-study comparisons between the 2 positive data sets presents challenges. “These are different trials, but when we need to pick a regimen, we do what we have to do, which is try to parse apart signals from the data,” he said. “The strength of IO/IO, as we all know, is that the tail of the curve for durvalumab/tremelimumab is very nice. We don’t have that length of follow-up yet for atezolizumab/bevacizumab, but the response rate is clearly higher.”

In terms of selecting patients for the HIMALAYA regimen vs the IMbrave 150 regimen, Yarchoan said, “If you need a response for someone with a lot of disease where you really need to get some disease control, I think from the available data it’s atezolizumab/plus bevacizumab.” However, he adds that for patients who are “VEGF ineligible—patients with very recent surgery, recent stroke, recent heart attacks, recent bleeds—those are the patients for whom there’s no question that durvalumab/tremelimumab is a compelling regimen.”

El-Khoueiry concurred, “I would follow the same approach where atezolizumab/bevacizumab is the go-to regimen with durvalumab/tremelimumab being the backup option. We’ll see how that regimen performs in real-world as well. That remains to be seen.”

The HIMALAYA combination was granted a priority review in April 2022 and the FDA is expected to decide on the application in the fourth quarter of 2022.8

COSMIC-312

Unlike HIMALAYA, data from the phase 3 COSMIC-312 (NCT03755791) failed to make meaningful gains with the novel combination of cabozantinib (Cabometyx) plus atezolizumab in the first-line setting. Approved as a single agent for patients with HCC who have been previously treated with sorafenib, when added to the immune checkpoint inhibitor, cabozantinib elicited mixed results.9,10

At a median follow-up of 15.8 months, data showed the combination produced a clinical benefit in PFS; however, that benefit did not extend to OS. Investigators enrolled 837 patients and randomly assigned them to the cabozan-tinib/atezolizumab arm (n = 432), sorafenib arm (n = 217), or cabozantinib alone (n = 188). The median PFS was 6.8 months (95% CI, 5.6-8.3) with the investigative combination vs 4.2 months (99% CI, 2.8-7.0) with sorafenib (HR, 0.63; 95% CI, 0.44-0.91; P = .0012). At the interim analysis for OS, the median OS was 15.4 months (96% CI, 13.7-17.7) compared with 15.5 months (96% CI, 12.1-not estimable) in the combination and sorafenib groups, respectively (HR, 0.99; 95% CI, 0.69-1.48; P = .44).10

“COSMIC-312 was a bit of a disappointment to many of us,” Yarchoan said. “The study was positive regarding PFS, which was one of the coprimary end points, but missed the OS end

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Table: Updated IMbrave 150 Efficacy Data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atezolizumab/bevacizumab (n = 336)</th>
<th>Sorafenib (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>19.2 (17.0-23.7)</td>
<td>13.4 (11.4-16.9)</td>
</tr>
<tr>
<td>12-month OS rate</td>
<td>67%</td>
<td>56%</td>
</tr>
<tr>
<td>18-month OS rate</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.9 (5.7-8.6)</td>
<td>4.3 (4.0-5.6)</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>30% (25%-35%)</td>
<td>11% (7%-17%)</td>
</tr>
<tr>
<td>PR</td>
<td>8%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>18.1 (14.6-NE)</td>
<td>14.9 (14.9-17.0)</td>
</tr>
<tr>
<td>Response ≥ 12 months</td>
<td>69%</td>
<td>65%</td>
</tr>
<tr>
<td>Response ≥ 18 months</td>
<td>51%</td>
<td>22%</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.
point. The OS curves were at least, thus far, overlapping with the sorafenib curves. I’m not quite sure what happened. Cabozantinib is a very active agent in HCC. It’s an agent that I think many of us use in the second line where it performs very well.”

In terms of response, cabozantinib/atezolizumab elicited an objective response of 11% (95% CI, 8.1%-14.2%) compared with 4% (95% CI, 1.6%-7.1%) with sorafenib. The median time duration of response was 10.6 months vs 8.8 months, respectively, and median time to progression was 7.0 months vs 4.6 months.8

“The response rate of 11% is numerically lower than we’ve seen with PD-L1 monotherapy,” Yarchoan added. “Although the challenge here is that the sorafenib arm also had a very low response rate of approximately 4%, which is lower than we’ve seen in other recent studies, which were in the range of 15%. I don’t know if the radiology [was different], if there was stage migration, for example treating patients who had TACE [transarterial chemoembolization] lesions that may be less likely to show true response.”

Yarchoan noted that with other agents showing an OS benefit in the front line, the combination will not move forward. Other studies, including the phase 3 LEAP-002 trial (NCT03713593), evaluating pembrolizumab (Keytruda) in combination with lenvatinib also failed to demonstrate a significant improvement in OS vs lenvatinib alone.11

“It seems unlikely that any of those are going to displace the current standard,” Bekaii-Saab said. “As exciting as it is to see another phase 3 trial, I don’t know if it’s going to break that ceiling.”

**TKIs STILL HOLD A ROLE**

Despite the combination therapies outperforming single-agent sorafenib in phase 3 trials, there is still a place for TKIs for select patient populations. “We talk about IO/IO combinations, but we still have other elements in our armamentarium—the TKIs, such as lenvatinib or sorafenib. Who are the patients for whom you would pick one of these TKIs as your first-line option?” Bekaii-Saab asked the panel.

Overall, El-Khoueiry said it would depend on the characteristics and patient preference. “The easy answer is patients who have clear contraindications to immunotherapy, those with active autoimmune disease,” he said. “There’s data indicating that patients with a distant history of autoimmune disease may be able to tolerate IO. It’s those with active autoimmune disease or disease that has required recent immunosuppression, who would be the bulk of patients who would get a TKI. Otherwise, I think it would be just a decision that an individual doesn’t want to have intravenous therapy or doesn’t want to travel for treatment. A TKI would be more convenient.”

In choosing the proper TKI for patients, Vogel said he would choose lenvatinib based on the “compelling” real-world data. “For 10 years we have used sorafenib [and] there is a time to change and try something new,” he said adding that sorafenib may still have a role for patients with Child-Pugh B status. “For those with good liver function, it’s lenvatinib.”

The evidence to support Vogel’s choice of lenvatinib comes from the REFLECT study (NCT01761266) in which the agent was evaluated against sorafenib. Overall, the agent was noninferior in terms of OS (HR, 0.92; 95% CI, 0.79-1.06); however, in an analysis characterizing outcomes based on characteristics, lenvatinib demonstrated early and durable response. The objective response among 478 patients was 18.5%, which investigators noted were comparable to the data reported with single-agent IO therapies.12
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.


VONJO™ is a trademark of CTI BioPharma Corp. ©2022 CTI BioPharma Corp. All rights reserved. US-PAC-2100040 03/2022
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. Intensify anti-diarrheal 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 anti-diarrheal 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 <30 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.

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. Co-administration 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 CYP3A2, 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 CYP3A2, CYP3A4, P-gp, BCRP, or OCT1.

ADVERSE REACTIONS

Fetal 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 fetal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningoencephalitis, 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 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).

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-200045 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. 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 no such adverse reactions in patients 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.

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 (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.

5.5 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.

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
Coadministration 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.
6 ADVERSE REACTIONS (cont.)
6.1 Clinical Trials Experience (cont.)

PERSIST-2 Trial

The safety of VONJO was evaluated in the randomized, controlled PERSIST-2 trial. In PERSIST-2, key eligibility criteria included adults with intermediate or high-risk primary or secondary (PPV or PET) MF with splenomegaly and a platelet count ≤100 × 10^9/L. Prior JAK inhibitor therapy was permitted. Patients received VONJO at 200 mg twice daily (n=106), 400 mg once daily (n=104), or best available therapy (BAT) n=98. Forty-seven (44%) of the 106 patients treated with VONJO 200 mg twice daily had a baseline platelet count of <50 × 10^9/L. The 400 mg once daily dose could not be established to be safe, so further information on this arm is not provided.

In PERSIST-2, among the 106 patients treated with VONJO 200 mg twice daily, the median baseline hemoglobin was 9.7 g/dL, and the median drug exposure was 25 weeks. Fifty-four percent of patients were exposed for 6 months, and 18% were exposed for approximately 12 months. Accounting for dose reductions, the average daily dose (mean relative dose intensity) and median daily dose (median relative dose intensity) were 380 mg (95%) and 400 mg (100%), respectively, for patients receiving VONJO twice daily.

The median age of patients who received VONJO 200 mg twice daily was 67 years (range: 39 to 85 years), and 56% were male, 38% were female, 3% were Asian, 2% were Native Hawaiian or Other Pacific Islander, 0% were Black, 9% did not report race, and 97% had an Eastern Cooperative Oncology Group performance status of 0 or 1.

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 ≥2% of 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%). Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with 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, meningoencephalitis, and acute myeloid leukemia in <1% of patients each, respectively.

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%).

Drugs interruptions due to an adverse reaction occurred in 27% of patients who received VONJO 200 mg twice daily compared to 10% of patients treated with BAT.

The most frequent reasons for drug interruption in ≥2% of patients receiving VONJO 200 mg twice daily were anemia (5%), thrombocytopenia (4%), diarrhea (3%), nausea (3%), cardiac failure (3%), neutropenia (2%), and pneumonia (2%).

Dosage reductions due to an adverse reaction occurred in 12% of patients who received VONJO 200 mg twice daily compared to 7% of patients treated with BAT. Adverse reactions requiring dosage reduction in ≥2% of patients who received VONJO 200 mg twice daily included thrombocytopenia (2%), neutropenia (2%), conjunctival hemorrhage (2%), and epistaxis (2%).

The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

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) (N=106)</th>
<th>Best Available Therapy (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades¹</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (4%)</td>
<td>4 (0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34 (32%)</td>
<td>32 (18%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (30%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (22%)</td>
<td>22 (15%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20 (19%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (14%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (10%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12 (11%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (10%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

¹ 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, lower 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 Cmax 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 antidiarrheal 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 not 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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US-PAC-2100050 02/2022
EphrinB2 Emerges as Targetable Option in Urothelial Carcinoma

by CHRISS RYAN

**TREATMENT WITH SOLUBLE** EphB4-human serum albumin (sEphB4-HSA) plus pembrolizumab (Keytruda) elicited synergistic activity and an improved overall survival (OS) and objective response rate (ORR) compared with historical data for PD-1/PD-L1 monotherapy in patients with platinum-refractory metastatic urothelial carcinoma, according to findings from a phase 2 trial (NCT02717156) published in the Journal of Clinical Oncology.

At a median follow up of 22.9 months (range, 1.3-54.7) in the intention-to-treat (ITT) analysis, the median OS was 14.6 months (95% CI, 9.2-21.5); the P value was .014 for rejecting the null hypothesis that the median survival would be 6.9 months or less. The median progression-free survival (PFS) was 4.1 months (95% CI, 2.7-27.9). The ORR was 52% (95% CI, 37%-67%), which included a complete response rate of 24% (95% CI, 12%-36%) and a partial response rate of 28% (95% CI, 15%-41%). The DCR was 80% (95% CI, 69%-92%). Notably, response was maintained at 6, 12, and 24 months in 88%, 74%, and 69% of the patients, respectively. The median duration of response (DOR) was not reached in either the ITT population or the EphrinB2-positive cohort.

Poor outcomes are associated with metastatic urothelial carcinoma following failure on standard frontline chemotherapy, and approved PD-1 inhibitors have low response rates in the second-line setting. EphB4 is highly expressed in urothelial cancer and leads to increased tumor cell invasion, proliferation, and survival. Interaction of high EphrinB2 in tumor vessels and EphB4 on tumor cells promotes angiogenesis and impedes immune cell traffic into the tumor. The combination of sEphB4-HSA and pembrolizumab can be administered with acceptable toxicity and improves key efficacy end points especially in [the] EphrinB2-HSA drug target.

In preclinical models, the combination of sEphB4 and PD-1 inhibition was more active than either agent alone, supporting further evaluation. In this phase 2 trial, 70 patients with metastatic urothelial carcinoma that recurred or progressed after platinum-based chemotherapy received sEphB4-HSA in combination with pembrolizumab. When stratified by PD-L1 status and EphrinB2 status, those with PD-L1-positive disease (n = 18) had an ORR of 61%. In this population 13 patients had EphrinB2-positive disease and an ORR of 69%. Among the EphrinB2-negative disease, the ORR was 40%. In the PD-L1 or unknown group (n = 52), the ORR was 29%. Those with EphrinB2-positive disease (n = 33) had an ORR of 45%; and those with EphrinB2-negative disease had an ORR of 0%. To be eligible for enrollment, patients had to be at least 18 years of age and have histologically confirmed urothelial carcinoma with disease progression after platinum-based chemotherapy for advanced disease or recurrence within 12 months of receiving platinum-based adjuvant or neoadjuvant therapy for localized muscle-invasive disease; at least 1 measurable lesion according to RECIST v1.1 criteria, and an ECOG performance status (PS) of 0 or 1.

Patients received 200 mg of intravenous (IV) pembrolizumab once on day 1 and 10 mg/m² of IV sEphB4-HSA once daily on days 1, 8, and 15 every 21 days. The regimen also had acceptable toxicity, and the tolerability monitoring boundary was not crossed, with a total of 11 events in 11 patients.

Additional results indicated that at a median follow-up of 22.5 months (range, 3.5-54.7) among the patients with EphrinB2 expression (n = 46), the median OS was 21.5 months (95% CI, 12.4-not reached), and the median PFS was 5.7 months (95% CI, 2.7-27.9). The disease control rate (DCR) was 66% (95% CI, 55%-77%).

**TABLE. Response Outcomes with Pembrolizumab and sEphB4-HSA**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All patients (n = 70)</th>
<th>Patients with EphrinB2-positive tumors (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>ORR</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>70</td>
<td>37%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>27</td>
<td>33%</td>
</tr>
<tr>
<td>≥65 years</td>
<td>43</td>
<td>40%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>46%</td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
<td>36%</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39</td>
<td>36%</td>
</tr>
<tr>
<td>1</td>
<td>31</td>
<td>39%</td>
</tr>
<tr>
<td>Histologic variant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>35%</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>41%</td>
</tr>
<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>44%</td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>17%</td>
</tr>
<tr>
<td>Disease site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower: bladder or urethra</td>
<td>56</td>
<td>36%</td>
</tr>
<tr>
<td>Upper: renal pelvis or ureter</td>
<td>14</td>
<td>43%</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>26</td>
<td>54%</td>
</tr>
<tr>
<td>2 to 4</td>
<td>44</td>
<td>27%</td>
</tr>
</tbody>
</table>

ORR, objective response rate.
The primary end points of the trial were tolerability and OS. The secondary end points were PFS, ORR, DOR, and toxicity.

The median age of participants was 67 years. Sixty-four patients received only 1 prior line of therapy; 6 patients received more than one line of therapy. Baseline sites of disease included the lymph nodes \( (n = 45; 64\%) \), lungs \( (n = 24; 34\%) \), liver \( (n = 18; 26\%) \), and bone \( (n = 9; 13\%) \).

Thirty-nine patients \( (56\%) \) had an ECOG performance status of 0 and 31 \( (44\%) \) patients had an ECOG performance status of 1. Stratification of Bellmunt risk demonstrated that 27\% of patients had no risk factors, 37\% had 1 risk factor, and 36\% had 2 or more risk factors. Fourteen \( (20\%) \) patients had upper-tract disease as their primary site of disease. Forty-six \( (66\%) \) patients were EphrinB2 positive.

The median duration of therapy was 15 weeks \( (\text{range}, 3-120) \). Eight patients remain on treatment, and 37 patients \( (60\%) \) discontinued treatment because of disease progression. Of the 25 patients who stopped treatment for reasons other than progressive disease, 15 remain without subsequent systemic treatment and 21 received subsequent systemic therapy.

Any-grade adverse effects (AEs) occurring in at least 10\% of patients included hypertension \( (74\%) \), fatigue \( (44\%) \), anemia \( (17\%) \), anorexia \( (13\%) \), headache \( (13\%) \), nausea \( (13\%) \), proteinuria \( (11\%) \), rash \( (11\%) \), hyperuricemia \( (10\%) \), increase in aspartate aminotransferase \( (\text{AST}; 10\%) \), and pruritus \( (10\%) \).

Six patients \( (8.6\%) \) discontinued treatment because of grade 3 toxicity: arthralgia \( (n = 1) \), edema \( (n = 1) \), abdominal pain \( (n = 1) \), and supraventricular tachycardia \( (n = 1) \), increase in AST and alanine aminotransferase \( (n = 1) \), and endocrine disorder \( (n = 1) \).

Four \( (6\%) \) patients died on treatment because of organ failure attributed to pembrolizumab \( (n = 1) \), aspiration pneumonia \( (n = 1) \), and overall decline in health and clinical progression of disease \( (n = 2) \). Five patients withdrew from the trial, and 6 patients discontinued therapy per the recommendation of the treating physician.

Hypertension was the most common toxicity attributed to sEphB4-HSA; 74\% of patients experienced any-grade hypertension, and 46\% had grade 3 or 4 hypertension.

Severe immune-related AEs included myositis in 1 patient, which resulted in death. Grade 2 pneumonitis occurred in 1 patient. Other immune-mediated AEs resolved with corticosteroids and without sequelae.

“A larger controlled phase 3 trial is required to confirm the efficacy signal observed in this study,” the study authors concluded. “A phase 2 study of this combination in metastatic urothelial carcinoma is under way, which includes a frontline cohort and an EphrinB2-positive biomarker-selected previously treated cohort (NCT04486781).”

REFERENCES


Have you seen the data for SARCLISA + Kyprolis® (carfilzomib) and dexamethasone?

Explore the full results of the IKEMA phase 3 trial at sarclisahcp.com
Pan-FGFR Inhibitor Seeks to Overcome Resistance Hurdles in Cholangiocarcinoma and Urothelial Carcinoma

by BRITTANY LOVELY

EARLY SENSITIVITY TO FGFR inhibition has improved outcomes for patients across tumor histologies; however, kinase domain mutations limit extended efficacy for select patients including those with intrahepatic cholangiocarcinoma or urothelial cancer. Primary and acquired mutations associated with clinical resistance highlight the need for therapeutic development to focus on preventing the activation of these oncogenic driver alterations.1,2

“Alterations in the FGFR pathway are prevalent in many solid tumors, [as well as] some hematological malignancies,” Mitesh J. Borad, MD, said in an interview with OncologyLive®. “One cancer where [FGFR2 fusions are] more prevalent [include] intrahepatic cholangiocarcinoma, where the prevalence is estimated in the 10% range in the intrahepatic subtype. There are also FGFR2 mutations, which are found in [approximately] 3% to 4% of [tumors], mostly in the intrahepatic [subtype]. In bladder cancer, the alterations are mostly with FGFR3, and they’re most commonly mutations in exon 7 and exon 10.” Borad noted that there have been varying estimates reported in the 20% to 40% range depending on the subset of bladder cancer, Borad is a medical oncologist at Mayo Clinic Comprehensive Cancer Center in Phoenix, Arizona.

Identifying patients with these mutations has presented significant improvements in clinical outcomes, according to Sameek Roychowdhury, MD, PhD.

“...When we identify gain-of-function, activating FGFR alterations, whether it be a fusion or a point mutation in cholangiocarcinoma or bladder cancer, that helps us identify a subset of patients who are likely to benefit from an FGFR-targeted kinase inhibitor,” Roychowdhury said in an interview with OncologyLive®, adding that patients without the mutations may not experience any benefit. Roychowdhury is an assistant professor in the Department of Internal Medicine and the Department of Pharmacology at The Ohio State University in Columbus.

Patients with intrahepatic cholangiocarcinoma or urothelial carcinoma represent 2 populations with approved FGFR inhibitors targeting FGFR2 and FGFR3, respectively.2,5 Approvals of agents such as infgratinib (Truseltiq) and pemigatinib (Pemazyre) for patients with cholangiocarcinoma with an FGFR2 rearrangement or fusion have shown overall response rates of 23% and 36%, respectively, with median durations of response ranging from 5 to 9 months, respectively.4,6 Nearly all patients (98%) treated had intrahepatic cholangiocarcinoma.

Erdafitinib (Balversa) in advanced or metastatic urothelial carcinoma with FGFR3 or FGFR2 alterations demonstrated an overall response rate of 40% with a median duration of 5.6 months according to updated data from the BCL2001 trial (NCT02365597) published in Lancet Oncology.6

Although overall response rates are below 40% for the approved indications, clinical benefit has been seen in other end points. “In cholangiocarcinoma, we are seeing anywhere from 70% to 80% of patients having some kind of clinical benefit,’ whether it’s a partial response or stable disease, they’re experiencing disease control. In bladder cancer, we’re seeing a benefit rate of approximately 40%, where patients are having partial responses and stable disease.”

FIGURE. Phase 1 Trial Design for FGFR2 or FGFR3 Mutant Solid Tumors2,10

Key inclusion criteria
- Aged ≥ 18 years
- Histologically or cytologically confirmed diagnosis of advanced-stage malignancy
- May have received prior FGFR inhibitor therapy or be FGFR inhibitor treatment-naïve
- Have measurable or evaluable disease per RECIST 1.1
- FGFR2 and/or FGFR3 gene alterations
- Willing to provide archived tumor tissue samples < 5 years old, if available, and/or undergo mandatory pretreatment tumor biopsy
- ECOG performance status 0 or 1
- Estimated life expectancy of ≥ 3 months

Part A: dose-escalation N = 45
Dose escalation 5 to 50 mg of KN-3248 taken orally once daily

Part B: dose expansion N = 75

Cohort 1
Patients with intrahepatic cholangiocarcinoma with FGFR2 alterations

Cohort 2
Patients with urothelial carcinoma with FGFR2 and/or FGFR3 alterations

Cohort 3
Patients with other solid tumors with FGFR2 and/or FGFR3 alterations

DLTs, dose-limiting toxicities; MTD, maximum-tolerated dose; RP2D, recommended phase 2 dose.

Primary endpoints
Part A
- Safety and tolerability
- DLTs
- MTD
- RP2D

Part B
- Antitumor activity

Secondary endpoints
Parts A and B
- Pharmacokinetics
**FOLLOWING THE MUTATION TRAIL**

Primary and acquired mutations observed with first-generation FGFR inhibitors have prompted investigators to pinpoint opportunities to react or circumvent their development. “Just like we’ve seen in lung cancer, where you start with the first-generation inhibitors, you understand the mechanisms of resistance, and then subsequently better drugs are developed and you can prolong that response or you can [begin to] sequence drugs as newer generation inhibitors are brought through the development pipeline,” Borad said. “What we understand with FGFR2 and FGFR3 is that the mechanisms of resistance can be on pathway or off pathway. When they’re on pathway, they may be mutations in FGFR2 or FGFR3 themselves, often polyclonal mutations where you have many clones in the tumor, each having different mutations. You can often determine this is happening by liquid biopsy analysis. When [this occurs] you need drugs that can cover a lot of these different mutations because there’s multiple mechanisms of pathway resistance.”

Gatekeeper and molecular brake mutations, such as V565F and N550H, respectively, of FGFR2 and FGFR3, can lead to resistance. “What we understand with FGFR2 and FGFR3 is that the mechanisms of resistance can be on pathway or off pathway. When they’re on pathway, they may be mutations in FGFR2 or FGFR3, themselves, often polyclonal mutations where you have many clones in the tumor, each having different mutations. You can often determine this is happening by liquid biopsy analysis. When [this occurs] you need drugs that can cover a lot of these different mutations because there’s multiple mechanisms of pathway resistance.”

Gatekeeper and molecular brake mutations, such as V565F and N550H, respectively, have demonstrated an ability to escape inhibition with available FGFR inhibitors. Further, acquired bypass resistance mechanisms result in limited long-term efficacy for patients with cholangiocarcinoma and urothelial cancer.

“The average time to progression is approximately 6 months,” Roychowdhury said. “The [emerging] mutations tend to interfere with how the [FGFR] inhibitor interacts with the kinase part of the receptor. But we’ve also seen other mechanisms [arise]—mutations and other genes and pathways—that tend to be downstream of the receptor. We often see evidence of MAPK or PI3K activation downstream after FGFR resistance develops.”

**OVERCOMING THE RESISTANCE HURDLE**

An all-encompassing approach to blocking outgrowth activity of FGFR resistance clones and mutations, investigators have initiated a phase 1 study (NCT05242822) to evaluate the preliminary efficacy of KIN-3248, a next-generation pan-FGFR inhibitor in individuals with advanced solid tumors harboring FGFR2 and/or FGFR3 gene alterations. The first patient in the trial was dosed in April 2022.

KIN-3248 was designed to treat patients with intrahepatic cholangiocarcinoma, UC, and other solid tumors. In preclinical studies, KIN-3248 demonstrated activity across a range of mutations that drive primary disease and acquired resistance to other FGFR inhibitors. For example, the agent has shown that it can inhibit the activation of the FGFR-MAPK pathway in cells that express FGFR2 gatekeeper mutations. KN-4802 is a multicenter, open-label, 2-part study that aims to enroll approximately 120 patients with advanced-stage solid tumors.

Patients must have confirmed FGFR2 and/or FGFR3 mutations by previous genomic analysis of tumor tissue or circulating tumor DNA. Patients can be naïve to, or pretreated with, FGFR inhibitors. “With targeted therapies, you want to focus on those patients who have these alterations and keep [the populations] somewhat broad during dose escalation to arrive at the doses you would use in phase 2 studies and potentially pivotal studies,” Borad explained. "The gatekeeper is a common pathway..." he said. "We initially design the protocols to include a range of doses..." However, Borad noted that "we are beginning to see that there are other mutations that drive primary disease and acquired resistance to other FGFR inhibitors. For example, mutations in FGFR2 and/or FGFR3 may be in the low percentage range." In this scenario, "we may see a broader range of activity," he said. "We need to keep an eye on these patients." The trial is open to enrollment.

REFERENCES

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 5-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/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-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 cough, breathlessness, 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.

Embry-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/anemia, 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, 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE/S-FU/LV n=117</th>
<th></th>
<th>ONIVYDE/S-FU/LV n=117</th>
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<th>S-FU/LV n=134</th>
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<td>Neutropenic fever/neutropenic sepsis♦</td>
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<td>Intravenous catheter-related infection</td>
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<td>Fatigue/asthenia</td>
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*NCI CTCA v4.0.
†Early diarrhea: onset ≤24 hours of ONIVYDE administration.
‡Late diarrhea: onset >1 day after ONIVYDE administration.
§Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
♦Includes febrile neutropenia.

**Cholinergic Reactions:** ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 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 CTCA v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥5% difference Grades 3–4 [severe] according to NCI CTCA 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%), hyponatremia (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, iraconazole, lopinavir, nefazodone, neflnavir, 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.

**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 overdosage of ONIVYDE.

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Exploring High-Intensity Focused Ultrasound as an Organ-Sparing Option for Prostate Cancer

by THOMAS P. FRYE, DO

THE DEFINITIVE TREATMENT OF prostate cancer has historically relied on whole-gland treatment. Advances in surgical techniques and radiation technology have improved upon these therapies, but significant urinary and sexual adverse effects remain. Men continue to seek less morbid and less invasive options.

Organ-sparing surgical treatments are well described and considered standard of care in the treatment of many cancers. Even within urologic oncology, organ-sparing surgeries are offered to patients with renal and bladder malignancies. It begs the question: are there organ-sparing options for men with prostate cancer?

PUSHING THE BOUNDARIES OF PROSTATE CANCER TREATMENT

The goals of organ-sparing treatment would be to offer long-term oncologic control and minimize the adverse effects of whole-gland treatment. The term to describe this is focal therapy and it puts an emphasis on quality of life. Opponents of this type of therapy have argued that prostate cancer is a multifocal disease and thus organ-sparing treatment is not appropriate. It is true that prostate cancer is multifocal, but it is also true that most men have an index lesion that is larger and higher grade, which drives the overall tumor biology. Secondary lesions are small and low grade, and as a result are cancer for which active surveillance is normally offered. Evidence from most studies suggests that at least 30% of men with prostate cancer have unilateral clinically significant disease that would be potentially suitable for focal therapy.

When considering organ-sparing surgeries, accurate tumor location becomes paramount. Advancements in prostate multi-parametric MRI (mpMRI) offer the ability to localize cancers like never before. Using a breast cancer analogy, the mpMRI is akin to mammography, and focal therapy, or prostate lumpectomy, is analogous to partial mastectomy.

Many different techniques are being studied as focal therapy, including high-intensity focused ultrasound (HIFU), cryotherapy, irreversible electroporation, radiotherapy, photodynamic therapy, laser interstitial therapy, gold nanoparticle photothermal, and water vapor.

HIFU has become one of the most adopted focal therapy techniques around the world. The technology gained more initial traction outside the United States, and was not approved by the FDA until 2015 to be used for the destruction of prostate tissue (not specifically prostate cancer). HIFU is an outpatient procedure performed under anesthesia. A transrectal ultrasound is used to map the prostate and plan what area of the prostate to treat. In addition, mpMRI images can be fused with the real-time ultrasound images for more accurate tumor localization. The high-intensity ultrasound waves kill tissue with both thermal and mechanical destruction.

TABLE. Evaluation of HIFU in Unilateral Prostate Cancer

<table>
<thead>
<tr>
<th>Patient characteristics</th>
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<tbody>
<tr>
<td>Median age</td>
<td>64.8 years</td>
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<tr>
<td>Mean PSA</td>
<td>6.2 ng/mL</td>
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<tr>
<td>Low-risk disease</td>
<td>68%</td>
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<tr>
<td>High-risk disease</td>
<td>32%</td>
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<th>Outcomes</th>
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<tr>
<td>No CSC in treated lobes</td>
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<tr>
<td>No CSC in contralateral lobes</td>
</tr>
<tr>
<td>Mean PSA at 2 years</td>
</tr>
<tr>
<td>Radical TFS at 2 years</td>
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<tr>
<td>Radical prostatectomy</td>
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<tr>
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<tr>
<td>HIFU</td>
</tr>
<tr>
<td>Grade 3 AEs</td>
</tr>
<tr>
<td>12-month continence preservation rate</td>
</tr>
<tr>
<td>12-month erectile functions preservation rate</td>
</tr>
</tbody>
</table>

Although HIFU and focal therapy have been studied in all prostate cancer risk groups, most investigators in the field would agree that patients with intermediate-risk prostate cancer are the ideal candidates.

HIFU BY THE NUMBERS

Complications are rare but can include urinary retention, dysuria, hematuria, and urinary tract infection. An early study on HIFU focal therapy from France evaluated efficacy and quality-of-life outcomes of 111 patients. In this study, 97% of men remained continent and 78% of men had preserved erectile function (TABLE). Another trial, one of the largest trials of men undergoing HIFU focal therapy, reported on just over 1000 men in the United Kingdom. In this study, 81% of men were free from needing radical treatment at 96 months. A randomized trial comparing radical prostatectomy with focal therapy would be ideal to determine long-term efficacy; however, this is a difficult proposition for many reasons. A study such as this would require significant equipoise on the provider’s part, which may be problematic. In addition, based on statistical modeling, to show an overall benefit between the 2 treatments, an estimated 2000 to 8000 patients would need...
to enroll in such study. Finally, because prostate cancer is typically a slow-growing disease, patients would need to be followed for at least 10 to 15 years.

While the feasibility of a randomized trial is being debated, a propensity score-matched analysis to compare cancer control outcomes of focal therapy with radical prostatectomy has been done. Patients were matched 1:1 using numerous clinical measures, including year of treatment, age, prostate-specific antigen, Gleason score, stage, and cancer core length. The primary outcome was failure-free survival defined as transition to local salvage therapy or systemic therapy or development of metastases. Investigators reported that in patients with low/intermediate risk prostate cancer, oncological outcomes over 8 years were similar between focal therapy and radical prostatectomy.

The field of focal therapy for prostate cancer has advanced considerably over the last decade. Thus, many new questions have arisen, including the following:

• How do we select appropriate candidates?
• How do we best conduct follow-up to identify persistent or new prostate cancers?
• How do we treat recurrences?

It has created a paradigm shift in our true end point of treatment: preventing the development of nonlocalized disease compared with the historical treatment goal of cure. This provoking thought is perhaps best summarized by the quote from Willet F. Whitmore Jr, MD, who was chairman of the Urology service at Memorial Sloan Kettering Cancer Center in New York, New York, for more than 30 years:

“Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?”

REFERENCES


OCM Successor Puts Focus on Equity in Cancer Care—With Fewer Dollars for Services

by MARY CAFFREY

DAYS BEFORE IT EXPIRED, CMS announced a replacement for the Oncology Care Model (OCM) that officials say will put more focus on health equity—by less money to offer services that physicians say have improved patients’ lives.

The OCM, launched in 2016, ended June 30 amid calls for an extension and praise from oncologists who say they will never return to the old way of delivering care. Despite the OCM’s flaws, practice leaders say they have learned a lot, which they see reflected in the successor, the Enhancing Oncology Model (EOM), announced on June 27, 2022.1,2

However, the EOM will not start until July 2023, creating a yearlong gap for practices that took part in the OCM and relied on it to report quality measures to Medicare. Now, these practices will be required to report through the Merit-based Incentive Payment System (MIPS), which serves as a fallback option for any practice that receives Medicare payments but does not participate in an advanced alternative payment model (APM). A 2015 law overhauling Medicare reimbursement requires quality reporting under either MIPS or an APM. 3,4

Early reviews of the EOM are mixed. The EOM comes with significant new reporting requirements, which will track demographic information and how well practices deliver care when patients have “health-related social needs.” Monthly payments that OCM practices used to fund new services—such as patient navigation—will be cut 56% for each Medicare patient and 37% for those receiving both Medicare and Medicaid.5

“There are stark inequities in the ability of people with cancer across race, gender, region, and income to access cancer screening, diagnostics, and treatment,” said CMS Administrator Chiquita Brooks-LaSure in a news release.1 “CMS is working to advance President Biden’s Cancer Moonshot goals by helping Medicare cancer patients better navigate a challenging and often overwhelming journey. The EOM will incentivize participating oncology practices—including those in rural and underserved areas—to improve the provision of high quality, coordinated care that addresses patients’ social needs and improves patient and caregiver support.”

When the EOM was unveiled, Ted Okon, MBA, executive director of the Community Oncology Alliance (COA), said the group was “disappointed” with both the plan to cut monthly payments and with the yearlong gap between the 2 models. “During this time, practices will have to shoulder the extensive investments and operational changes put in place to benefit patients without reimbursement,” he said.3

In the weeks that followed, Okon reacted strongly to additional CMS proposals that will cut the Medicare conversion factor by 4.42%, along with “additional cuts to oncology, imaging, and radiation.”4 Finally, COA blasted a separate plan that would halt reforms to the 340B drug discount program, which community oncologists say have pushed too many independent practices into mergers or buyouts from hospitals.7

The net result, some community oncologists say, is that the EOM could be a tough sell to practices that lack experience in delivering value-based care. Larger community oncology networks that had mastered the OCM in its final years will still have to navigate the financial pieces with care. As Okon stated, COA fully supports screening for social needs and collecting patient-reported data; however, “it seems unfair to burden practices with more work but pay less for it.”

LESSONS FROM THE OCM

The OCM, first proposed in 2015, created financial incentives for providers who offered a more complete set of cancer care services, with a focus on care coordination.7 The goal was to reward those who offered appropriate care—not necessarily the most expensive care. The model had several defining features:

• It required participating practices to offer several enhanced services, including 24/7 access to the patient’s medical records, use of a certified electronic health record, patient navigation, a documented care plan including survivorship care, and treatment that followed clinical guidelines.

• Practices had incentives to keep patients out of the hospital and the emergency department (ED). Using technology, many developed sophisticated triage systems to respond to patient calls. Practice schedules were revamped to accommodate same-day, evening, or weekend appointments. More attention was paid to services, such as nutrition, that help keep patients out of the ED.

• Practices had to develop systems for tracking and reporting patient quality data, which were needed for reimbursement.

• Reimbursement through the OCM came through 2 streams: Practices received monthly MEOS payments based on episodes of care. Performance-based payments were made retroactively, based on measures of a practice’s ability to deliver quality care and achieve savings. Over time, practices were encouraged to take on “downside” risk in this second stream—meaning they would owe Medicare money if they fell short of benchmarks.

Leading oncology practices have said that the OCM, though far from perfect, propelled them forward to make strides in practice transformation that would have been harder to achieve without Medicare’s leadership. Many commercial payers have developed versions of the OCM, and few can envision returning to care without services such as patient navigation or care planning.

Both sides improved over time. A chief criticism of the OCM is that it failed to save enough money for Medicare.7 Large community oncology networks dispute this claim, arguing that the bad
reviews were based upon outcomes during the model’s early years, before practices developed efficiencies to administer it well.

During a recent webinar, leaders from The US Oncology Network said that the OCM had brought $240 million in savings for Medicare going into 2020, and the network had seen a 24% drop in ED visits and a 37% decrease in hospitalizations.8

At the same time, CMMI tweaked the model to address complaints that payment structures were not keeping pace with drug development, shortchanging those practices that hewed to guideline-directed care.

WHAT’S NEW UNDER THE EOM

Physicians have acknowledged that the next incarnation of the model should address health equity, and Kashyap Patel, MB, president of COA, supported this change when CMMI announced its “refresh” of APMs in 2021. “So far, models have focused on cost, quality, and patient experience. [Adding] equity as one of the factors is a welcome change,” Patel said in a news release.11

The EOM is proposed to run for 5 years through June 2028. It retains some key elements of the OCM; notably, it will be voluntary, not mandatory. It retains the basic structure, with 6-month care episodes and requirements for enhanced services, as well as the 2 reimbursement streams: monthly payments tied to episodes of care, and performance-based payments based on quality measures and demonstrated savings.

However, there are some important differences. In the biggest change, the EOM applies only to Medicare patients undergoing chemotherapy for common cancer types: breast cancer, chronic leukemia, lung cancer, lymphoma, multiple myeloma, prostate cancer, and small intestine/colorectal cancer. In contrast, the OCM covered nearly all types of cancer, with certain low-risk patients excluded. For example, the EOM will not cover patients with low-risk breast and low-risk colorectal cancer. In contrast, the OCM covered nearly all types of cancer, with certain low-risk patients excluded. For example, the OCM will not cover patients with low-risk breast and low-risk colorectal cancer. Under the OCM, a low-risk cancer patient who had a heart attack or joint replacement—and received that care elsewhere—could hurt the oncology practice’s performance.

Attribution. The EOM attempts to resolve a top physician complaint: When a patient sees many specialists, which practice includes that top physician complaint: When a patient sees many specialists, which practice included that patient in their roster of care episodes? Under the new program, if no practice provides 25% of all cancer-related evaluation and management (E/M) services for a patient during a 6-month episode, then the practice receiving attribution for that patient will have provided the plurality of E/M episodes.

Patient-reported outcomes. As expected, the EOM will add requirements for practices to collect electronic patient-reported outcomes. And in a consumer-friendly move, no co-payments will be required for patients to receive enhanced services.

Taking on 2-sided risk. Risk arrangements will start with a benchmark, which is an estimated amount of cost for all episodes in a 6-month period. All practices enrolled in the EOM will be required to take on some “downside” risk; however, the program offers 2 different options:

- Risk Arrangement 1, a lower-risk tier, will offer a limited level of performance-based reimbursement while limiting losses. According to information from CMMI, the stop loss will be capped at 2% of the benchmark, while the stop gain will be capped at 4%.

- Risk Arrangement 2, a higher-risk tier, offers greater reimbursement potential with more risk of repaying Medicare if benchmarks are not met; stop loss can reach 6% of benchmark, while the stop gain can reach 12%.

The first tier may appear to be the best option for practices that are less experienced in value-based care, but there’s a catch: The lower-risk tier will not qualify as an APM, and these practices will still have to report under MIPS.12

ADDRESSING HEALTH EQUITY IN CANCER CARE

As expected, a major focus of the EOM is addressing health equity: The model will include additional payments to oncology practices for patients who qualify for both Medicare and Medicaid. Practices must report demographic data and outline plans to address health equity.

Oncologists and practice leaders were surprised that the base MEOS payments will drop from $160 to $70. For dually eligible patients, MEOS payments will be $100 per month.1,12

Practices have until September 30 to apply for the EOM, and it remains to be seen if the proposed reimbursement scheme will attract new participants. Already, CMS has seen the faltering of one highly touted evidence-based model—the Medicare Diabetes Prevention Program—when too few providers enrolled. Diabetes education advocates warned that this would happen because the reimbursement schedule was inadequate, given administrative costs.13

“Community oncology practices are fully committed to positive, patient-centered improvement of cancer care and look forward to supporting CMMI and practices to make the EOM a success,” Okon said. “The goals of the EOM are ones we wholeheartedly support, especially related to improving cancer health equity, electronic patient-reported outcomes, enhanced access to cancer screenings.”

This article has been edited for space. To read the full version and for references visit bit.ly/3q3b4ie.
ZEJULA is the only 1X daily oral PARP inhibitor monotherapy. ZEJULA delivered 2X the median PFS vs placebo in HRd PATIENTS.¹⁻⁴

HRd = homologous recombination deficient; PARP = poly (ADP-ribose) polymerase; PFS = progression-free survival.

**Indication**

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

**Important Safety Information**

**Myelodysplastic syndrome/acute myeloid leukemia** (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1,785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

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

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

**Posterior reversible encephalopathy syndrome (PRES)** occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reintroducing 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\textsuperscript{1,2}

**Study Design\textsuperscript{1,2}:** 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.


CI = confidence interval; CR = complete response; HR = hazard ratio; PR = partial response.

Visit ZEJULAHCP.COM to explore the PRIMA data

Trademarks are property of their respective owners.
HZELA (niraparib) capsules, for oral use

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

1 INDICATIONS AND USAGE
1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

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

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

1.3.1 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

1.3.2 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

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6.1.1 Clinical Trials Experience

6.1.2 Clinical Trials Experience

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6.2.1 Post-Marketing Experience

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7.2 Pharmacokinetics

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8.1.2 Geriatric Patients

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8.2.1 Renal Impairment

8.2.2 Renal Impairment

8.2.3 Renal Impairment

8.3 Liver Impairment

8.3.1 Liver Impairment

8.3.2 Liver Impairment

8.3.3 Liver Impairment

8.3.4 Liver Impairment

8.4 Women of Childbearing Potential

8.4.1 Women of Childbearing Potential

8.4.2 Women of Childbearing Potential

8.4.3 Women of Childbearing Potential

8.4.4 Women of Childbearing Potential

8.4.5 Women of Childbearing Potential

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9.4 Drug Interactions

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10.1 Reproduction Studies

10.1.1 Reproduction Studies

10.1.2 Reproduction Studies

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10.2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

10.3 Toxicity and refactoriness

10.3.1 Toxicity and refactoriness

10.3.2 Toxicity and refactoriness

10.3.3 Toxicity and refactoriness

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11.5 Pharmacokinetics

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12.5 Clinical Studies

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15.1 Dosage Forms and Strengths

15.2 Dosage Forms and Strengths

15.3 Dosage Forms and Strengths

15.4 Dosage Forms and Strengths

15.5 Dosage Forms and Strengths

15.6 Dosage Forms and Strengths

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16.1 How Supplied/Storage and Handling

16.2 How Supplied/Storage and Handling

16.3 How Supplied/Storage and Handling

16.4 How Supplied/Storage and Handling

16.5 How Supplied/Storage and Handling

16.6 How Supplied/Storage and Handling

BRIEF SUMMARY OF PRESCRIBING INFORMATION

ZEJULA (niraparib) capsules are supplied as 100 mg capsules.

Warnings and Precautions

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

5.2 Bone Marrow Suppression

5.3 Myeloid Neutrophilia

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5.5 Embryo-Fetal Toxicity

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6.3 Laboratory Tests

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6.7 Other Reactions

Appendix B: Descriptions of Adverse Reactions

Table 1: Adverse Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA

Table 2: Adverse Reactions Reported in ≥2% of Patients Receiving ZEJULA in QUADRA
Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA. Permanent discontinuation in >2% of patients who received ZEJULA was due to adverse reactions.

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count: Among patients who received ZEJULA with the dose based on weight and 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 occurred 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 group of patients who received ZEJULA.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n=244)</th>
<th>ZEJULA (n=169)</th>
<th>Placebo (n=86)</th>
<th>ZEJULA (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54 5</td>
<td>21 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>50 28</td>
<td>23 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36 8</td>
<td>15 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28 11</td>
<td>5 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53 21</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>31 15</td>
<td>1 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 9</td>
<td>0 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48 36</td>
<td>3 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19 5</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22 17</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 13</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21 14</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>12 5</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18 10</td>
<td>0 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 9</td>
<td>5 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, or 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.

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 6: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n=169)</th>
<th>ZEJULA (n=367)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61 5</td>
<td>29 0.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>50 7</td>
<td>25 0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36 20</td>
<td>2 2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17 8</td>
<td>5 0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>10 2</td>
<td>0 0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>74 35</td>
<td>3 1</td>
</tr>
<tr>
<td>Constipation</td>
<td>40 20</td>
<td>0.8 2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 16</td>
<td>2 0.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 6</td>
<td>0.5 0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18 12</td>
<td>0 0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10 4</td>
<td>0.3 0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>57 41</td>
<td>8 0.6</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 15</td>
<td>0.3 0.6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13 8</td>
<td>0.8 1</td>
</tr>
</tbody>
</table>

The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hyperkalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, white blood cell count decreased, hypertension. ASALT=Aspartate transaminase/alanine aminotransferase.
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

- Neutropenia includes events with preferred terms of neutropenia.
- Thrombocytopenia includes events with preferred terms of thrombocytopenia.
- Anemia includes events with preferred terms of anemia, hemoglobin normocytic anemia.

Cough 13 0
Dizziness 11 0
Headache 19 0.4
Musculoskeletal and connective tissue disorders

- Blood alkaline phosphatase increased
- AST/ALT elevation

Metabolism and nutrition disorders

- Decreased appetite
- Musculoskeletal and connective tissue disorders

Musculoskeletal pain 29 3
Nervous system disorders

- Headache
- Dizziness

Psychiatric disorders

- Insomnia

Renal and urinary disorders

- Acute kidney injury
- Respiratory, thoracic and mediastinal disorders

Dyspnea 22 3
Cough 13 0
Vascular disorders

- Hypertension

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. Approve pregnant women of the potential risk to a fetus.

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

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed child 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).

17 PATIENT COUNSELING INFORMATION

Advisers 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)].

Bone Marrow Suppression

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

Hypertension and Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first 2 months, then monthly for the first year of treatment and periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated [see Warnings and Precautions (5.2)].

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 in the morning or evening. Advise patients that if they miss a dose of ZEJULA not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

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

Contraception

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

Lactation

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

Allergic Reactions to FDAC Yellow No. 5 (Tartrazine)

Advise patients that ZEJULA capsules contain FDAC 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:IBRS 03/2021

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**Intraperitoneal Chemotherapy Technique Aims to Dramatically Improve Outcomes in Gastric Carcinomatosis**

*by KYLE DOHERTY*

**PATIENTS WITH ADVANCED** gastric cancer that has progressed to gastric carcinomatosis have traditionally lacked effective treatment options with a poor survival outlook. However, a novel approach to chemotherapy administration in the disease space is poised to alter the treatment landscape and improve outcomes for this patient population.

The phase 2 STOPGAP trial (NCT04762953) will assess the safety and efficacy of sequential chemotherapy administered intravenously followed by intraperitoneal chemotherapy with paclitaxel. This approach has not been evaluated for patients with stage IV gastric cancer that has progressed to gastric carcinomatosis in the United States.

"In gastric cancer, the likelihood of peritoneal carcinoma is very high compared with other gastrointestinal malignancies; it is approximately 30% to 50%," Maheswari Senthil, MD, FACS, said in an interview with OncologyLive®.

"The unique aspect of peritoneal carcinomatosis is that the peritoneum is a [highly] protected cavity. The penetration of [the peritoneal cavity with] chemotherapy agents is limited because of the blood-peritoneal barrier. Although systemic chemotherapy administered intravenously is extremely important, it may not have adequate penetration to treat the carcinomatosis part of the disease."

Senthil is the principal investigator on the STOPGAP trial. She is also the director of the Peritoneal Malignancy Program at the Chao Family Comprehensive Cancer Center, chief of the Division of Surgical Oncology, and a clinical professor of surgery at the school of medicine at the University of California, Irvine.

Palliative intravenous chemotherapy and/or best supportive care is the current standard for patients with gastric peritoneal carcinomatosis. The median overall survival (OS) for this patient population is approximately 7 months. In a retrospective analysis by Rau et al, 19 patients with peritoneal metastases of gastric cancer treated between August 2008 and December 2017 received systemic chemotherapy alone. These patients experienced a median OS of 4.9 months, and the 1-year survival rate was 0%.1

**INTERNATIONAL FINDINGS WITH INTRAPERITONEAL CHEMOTHERAPY ARE PROMISING**

Intraperitoneal chemotherapy for gastric cancer with peritoneal carcinomatosis has been evaluated in multiple clinical trials in Asia. A phase 2 clinical trial from Singapore and Japan has evaluated the safety and efficacy of intraperitoneal paclitaxel as well as intraperitoneal docetaxel.2

In this study, 40 patients received intraperitoneal paclitaxel at a dose of 20 mg/m² and 50 mg/m² of intravenous paclitaxel administered on days 1 and 8. The oral fluoropyrimidine derivative S-1 was also given at a dose of 80 mg/m² daily for 14 consecutive days, followed by 7 days of rest. Patients experienced a median OS of 22.6 months, with a 1-year OS rate of 78%.3

Findings from Yamaguchi et al showed that the same treatment regimen administered to 35 patients elicited a median OS of 17.6 months, with a 1-year OS rate of 77% and a 2-year OS rate of 45%.

Imano et al reported findings from an intensive paclitaxel regimen—intraperitoneal paclitaxel at 80 mg/m² followed by S-1 80 mg/m² daily for 14 consecutive days. Intravenous paclitaxel 50 mg/m² was given on days 1 and 8. The median OS was 21.3 months and the 1-year and 2-year OS rates were 69% and 46%, respectively.4 Finally, in results from Fushida et al and Fujiwara et al, intraperitoneal docetaxel administered in doses ranging from 35 mg/m² to 60 mg/m² in combination with S-1, the median OS was 24.6 months and 16.2 months, respectively.

In terms of tolerability, Senthil noted that no unique trends in adverse effects were reported with intraperitoneal administration. "Extrapolating the data from the Asian studies that have extensively used paclitaxel for intraperitoneal administration, this is a very well-tolerated treatment," she said. "[Additionally], some patients in the Asian studies received [intraperitoneal chemotherapy] for multiple cycles—[some up to 20 cycles], just repeated intraperitoneal administration. The tolerability and extension of use of intraperitoneal chemotherapy could be even more than what we are projecting in STOPGAP."

Following these encouraging phase 2 data, Japanese investigators initiated the phase 3 PHOENIX-GC trial (UMIN000005930) in patients with gastric cancer with peritoneal metastasis. In the study, the efficacy of intraperitoneal paclitaxel plus systemic S-1 and paclitaxel (n = 114) was compared with standard systemic chemotherapy (n = 50). Patients enrolled in the trial had received no prior therapy or short-term chemotherapy defined as less than 2 months. The primary end point was OS and secondary end points included overall response rate and safety.4

Findings from the trial showed that the median OS in the investigational arm was 17.7 months (95% CI, 14.7-21.5) compared with 15.2 months (95% CI, 12.8-21.8) in the control arm (HR, 0.72; 95% CI, 0.49-1.04; P = .08). The 3-year OS rates were 21.9% (95% CI, 14.3%-29.9%).

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**FIGURE. STOPGAP Phase 2 Trial Design**

**Key inclusion criteria**
- Histologically or cytologically confirmed primary gastric or gastroesophageal adenocarcinoma
- Received a minimum of 3 months of systemic treatment without visceral metastatic progression in the first-line setting
- Peritoneal cytology positive disease or peritoneal carcinomatosis detected by imaging, laparoscopy, or laparotomy
- Age 18 to 75 years
- ECOG performance status ≤2
- Life expectancy of > 6 months
- Adequate organ and marrow function

**End points**

Primary
- PFS at 1 year
- Incidence of TEAEs

Secondary
- OS
- Patient-reported quality-of-life outcomes

**N = 35**

Patients will receive sequential intraperitoneal paclitaxel along with intravenous paclitaxel, fluorouracil, and leucovorin on days 1 and 8 of every 21-day cycle for 3 months.

OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse effect.
and 6.0% (95% CI, 1.6%-14.9%). Both regimens were well tolerated. The findings were maintained across subgroups with the largest benefit observed in those with moderate amount of ascites (HR, 0.38;95% CI, 0.16-0.90; P = .03) and women (HR, 0.55; 95% CI, 0.32-0.95; P = .03).

Study authors concluded that although the superiority in terms of OS of intraperitoneal paclitaxel plus systemic chemotherapy was statistically insignificant compared with the standard of care, exploratory analyses suggested potential clinical benefits of intraperitoneal paclitaxel in gastric cancer.

STOPGAP AIMS TO IMPROVE OPTIONS IN GASTRIC CANCER

The STOPGAP trial is currently recruiting, and investigators seeking to enroll approximately 35 adult patients with primary gastric or gastroesophageal adenocarcinoma with cytology-positive peritoneal lavage and/or peritoneal carcinomatosis. Eligible patients must have an ECOG performance status of 2 or less, adequate organ and marrow function as defined by investigators, and a life expectancy greater than 6 months (FIGURE). Patients will be excluded from the trial if they have received systemic treatment for more than 3 months preceding enrollment. Those who have undergone prior surgery that would preclude safe diagnostic laparoscopy and port placement, have evidence of a distant solid organ metastasis, or have an active infection that mandates systemic therapy are also not eligible.

“STOPGAP will help us truly understand the subgroup of patients [with gastric cancer] for whom we are able to [generate] the maximum effect in their OS,” Senthil said. “That would help us create even more knowledge about which set of patients benefit from this approach. Then [we would] be able to design the next clinical trial that highly selects for these patients with certain predictive markers, and clinical features that are necessary to derive the most benefit.”

Initially, patients in the single-arm, nonrandomized, open-label trial will receive systemic therapy for 3 months at the clinician’s discretion based on molecular biomarkers. Patients will then undergo diagnostic laparoscopy followed by intraperitoneal port placement. Investigators will treat patients with an intravenous chemotherapy regimen of paclitaxel, fluorouracil, and leucovorin. Paclitaxel will also be instilled into the peritoneal cavity through the intraperitoneal port at a dose of 40 mg/m². Treatment will be administered on days 1 and 8 of each 21-day cycle for 3 months.

Four to 6 weeks following the completion of intraperitoneal chemotherapy, restaging imaging will be performed using CT scan and/or diffusion-weighted MRI with contrast. Diagnostic laparoscopy will also be used to assess peritoneal disease burden and treatment response. Patients will then be assigned to a treatment plan based on their response to treatment and extent of disease. If a patient experiences stable disease or a response and a peritoneal cancer index (PCI) score greater than 10, they will continue treatment with the intraperitoneal chemotherapy regimen; patients with disease progression will transition to a second-line regimen; and patients with a response and a PCI score of 10 or less for whom complete cytoreduction is feasible will be considered for cytoreduction with intraperitoneal chemotherapy.

The primary end points of the study are 1-year PFS. Secondary end points include OS and patient-reported quality-of-life outcomes. Other outcome measures include expression of plasma and ascites exosomal gene signature (EXOSIG) and EXOSIG to treatment response. Study authors estimate that the trial will be completed in June 2025.

“There are implications from this study that could be extrapolated to other cancers,” Senthil said. “The general concept of normothermic intraperitoneal chemotherapy is something that we will take away from the study. Right now, normal thermic intraperitoneal chemotherapy is not routinely administered in patients with carcinomatosis, then we should be expanding this approach to other diseases for which it can be applied. I am looking forward to a future where we can customize treatment approaches for individual patients.”

The trial is open for enrollment.

REFERENCES


“The unique aspect of peritoneal carcinomatosis is that the peritoneum is a [highly] protected cavity. The penetration of [the peritoneal cavity with] chemotherapy agents is limited because of the blood-peritoneal barrier. Although systemic chemotherapy administered intravenously is extremely important, it may not have adequate penetration to treat the carcinomatosis part of the disease.”

—MAHESWARI SENTHIL, MD, FACS
Updated NCCN Guidelines Grant Tivozanib Category 1 Status for Pretreated RCC

by CAROLINE SEYMOUR

THE KIDNEY CANCER TREATMENT GUIDELINES, housed within the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, have been revised, granting tivozanib (Fotivda) Category 1 status as a subsequent therapy for patients with renal cell carcinoma (RCC) who have received at least 2 prior lines of treatment, according to an announcement from AVEO Oncology.1,2

On March 10, 2021, the FDA approved tivozanib for the treatment of adult patients with relapsed/refractory advanced RCC following 2 or more prior systemic therapies.3 The approval was based on findings from the phase 3 TIVO-3 trial (NCT02627963). Tivozanib demonstrated a significant improvement in progression-free survival (PFS) compared with sorafenib (Nexavar), with similar overall survival (OS) in patients with highly relapsed/refractory metastatic RCC.4

The controlled, multicenter, open-label, phase 3 trial randomized 350 patients with highly refractory metastatic RCC who had failed 2 or more prior regimens, including VEGFR-TKI treatment, 1:1 to receive oral tivozanib or sorafenib. Crossover between arms was not permitted.

Primary findings from the study demonstrated an increased independent review committee–assessed median PFS for tivozanib compared with sorafenib at 5.6 months vs 3.9 months, respectively (stratified HR, 0.73; 95% CI, 0.56-0.95; P = .016). The final hazard ratio (HR) for OS was 0.97 (95% CI, 0.75-1.24; P = .78).

Findings from an exploratory analysis from the study presented at the 2022 Genitourinary Cancers Symposium demonstrated that the investigator-assessed HR for PFS favored tivozanib compared with sorafenib (HR, 0.624; 95% CI, 0.49-0.79). That result was comparable to the primary IRC-assessed HR for PFS (unstratified HR, 0.672; 95% CI, 0.52-0.87).5

Additionally, landmark long-term PFS rates were significantly higher with tivozanib vs sorafenib, at 12.3% and 2.4%, respectively, at 3 years, and 7.6% and 0%, respectively, at 4 years. Moreover, mature OS data also reflected a nonsignificant trend in continued favor of tivozanib (HR, 0.89; 95% CI, 0.70-1.14).6

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

ASTRO Releases Clinical Guidelines for Radiation Therapy in IDH-Mutant Glioma

by JASON HARRIS

FOR THE FIRST TIME, the American Society for Radiation Oncology (ASTRO) has issued recommendations on the use of radiation therapy to treat patients with IDH-mutant grade 2 and grade 3 diffuse glioma, including oligodendroglioma and astrocytoma.1,2

The recommendations provide guidance on optimal radiation dosing, treatment planning, delivery techniques, and survivorship based on tumor histology and grade. Generally, the recommendations call for close observation following surgery for patients with lower-risk disease. ASTRO recommends adjuvant therapy for patients with any features of higher-risk glioma.

The World Health Organization (WHO) in 2021 reclassified gliomas to reflect the discovery of new biomarkers, including mutations to the genes that encode IDH enzymes. Doing so caused ASTRO to rethink the best ways to treat patients included in the new classifications.

According to findings published in 2021 prior to the most recent reclassification, glioma accounts for 80.7% of malignant brain tumors in the United States.3 In an assessment of primary brain tumors diagnosed from 2010 to 2014, the average annual age-adjusted incidence rate was 6.0 per 100,000 population. Glioma incidence varies greatly by age, sex, and race or ethnicity, but incidence is highest among non-Hispanic White men and women. The 5-year survival rate for glioblastoma, the most common form of glioma, is approximately 5%.4

“For patients diagnosed with low-grade glioma, clinical trials show improved survival outcomes with a variety of treatment approaches,” Helen A. Shih, MD, MPH, chair of the guideline task force, director of the CNS & Eye Service in the Department of Radiation Oncology at Massachusetts General Hospital (MGH), and medical director of the MGH Proton Therapy Centers, said in a news release. “The heterogeneity of patient cohorts in these trials and the use of a now-outdated tumor grading system also can make it difficult to draw conclusions for patient care without clear guidance based on the new WHO classification.”

Results from clinical trials conducted in the United States show significant differences in care patterns in the use of radiation therapy in this patient population. ASTRO officials speculated those differences could be attributed to lack of definitive overall survival benefit in randomized trials and central recommendations.

The multidisciplinary guideline task force based its recommendations on a systematic literature review of articles published through July 2020. The guideline addresses clinical management of adverse effects (AEs) and includes an algorithm that summarizes the treatment paths.

The guideline also offers recommendations on survivorship care including multidisciplinary approaches to assess and manage treatment-related AEs. The task force emphasizes the importance of lifelong surveillance to detect recurrences and late AEs for patients diagnosed with these tumors.

REFERENCES


Bispecific Antibody ABBV-383 Looks to Fill Unmet Need in Heavily Pretreated Multiple Myeloma

by BRITTANY LOVELY

PROMISING SAFETY AND EFFICACY results were observed with the novel bispecific antibody ABBV-383 in patients with heavily pretreated relapsed or refractory multiple myeloma, according to updated results from a phase 1 trial (NCT03933735) presented at the 19th International Myeloma Society Annual Meeting.1

Among 38 evaluable patients in the dose-expansion and dose-escalation cohorts to receive ABBV-383 at 60 mg, the objective response rate (ORR) was 60% and the median duration of response (DOR) was not reached (NR; 95% CI, NR-NR). A very good partial response (VGPR) rate or better was reported for 43% of responders with a complete or stringent complete response (CR/sCR) reported in 29%, a VGPR reported among 14%, and a partial response (PR) reported among in 17% of patients. The median time to first response was 0.8 months (range, 0.7-4.2) and the median time to first CR/sCR was 2.8 months (range, 1.4-12.0). The 12-month estimated response rate was 76.8% (95% CI, 55.1%-89.0%).

Investigators reported safety outcomes for all patients treated in the escalation and expansion cohorts to receive ABBV-383 at 60 mg (n = 60). Cytokine release syndrome (CRS) of any grade was observed in 72% of patients, with 48% of events being grade 1, 22% being grade 2, and 2% being grade 3 (FIGURE).1 Serious CRS was documented in 16 patients. These events occurred following the first dose and the median time to onset and resolution was 1 day with supportive care measures. No patients experienced recurrence after cycle 1. Of note, per study protocol the first dose of the agent is administered in the inpatient setting, which can allow for additional monitoring of CRS.

ABBV-383 is a novel investigational BCMA × CD3 T-cell-engaging bispecific monoclonal IgG4 antibody. It was designed to maximize off-target cell killing and minimize a toxicity associated with other T-cell-engaging agents brought on by the overstimulation of T cells.1,2

Peter Voorhees, MD, a hematologist/oncologist at the Atrium Health Levine Cancer Institute in Charlotte, North Carolina, noted 2 distinguishing features of the ABBV-383 in a presentation of the data. “[ABBV-383] harbors 2 BCMA binding domains to better engage its target and it also utilizes a lower affinity CD3 binding domain with the strategy [being to] try to mitigate the potential CRS [that] can occur with these therapeutics and potentially allow for full therapeutic dosing right from the beginning.”

TOXICITY PROFILE OF ABBV-383

A detailed portrait of CRS toxicity was presented for varying dose levels in the study. Premedications included intravenous dexamethasone 10 mg or equivalent in addition to diphenhydramine or equivalent, famotidine or equivalent, and acetaminophen or equivalent. These agents were administered 15 to 60 minutes prior to ABBV-383. Investigators noted that if CRS is not noted in a prior cycle, dexamethasone may be tapered.

Among the 15 patients who received ABBV-383 at 0.025 to 1.8 mg, 7% of patients reported CRS grade 2. Among those who received doses ranging from 5.4 to 30 mg (n = 28), 18% of patients had CRS grade 2 and 21% had CRS grade 1. Nine patients received doses ranging from 40 to 50 mg, with 22% having CRS grade 2 and 56% having CRS grade 1. “As far as CRS is concerned, it’s a dose effect: the more you give, the higher the likelihood of CRS,” Voorhees said. Among the 9 patients who received 90 mg, 67% experienced CRS (grade 1, 22%; grade 2, 33%; grade 3, 11%). At the 120 mg dose (n = 3), 1 patient had grade 3 CRS and 2 others had grade 1 CRS.

In an expanded safety analysis, Voorhees presented data for the 60-mg cohort as well as data for the entire treated population (n = 124). Serious AEs were reported in 58% of patients in the 60-mg cohort and 53% in the overall population. Three patients experienced immune effector cell-associated neurotoxicity syndrome, all of whom were treated with the 60-mg dose. Infection occurred in 43% of patients in the 60-mg cohort. Of the 41% of patients overall who experienced infections, 31% of patients experienced serious events and 24% of events were grade 3 or higher events and included pneumonia, sepsis, COVID-19, and urin ary tract infections.

“Treatment is ongoing in 45% of patients, and the overwhelming majority of [individuals] who discontinued treatment did not discontinue treatment because of AEs,” Voorhees noted, adding that 10 deaths were reported with the 60-mg dose. “Most of these occurred beyond 30 days with the last dose of drug [n = 10] and none were determined to be related to ABBV-383,” he said. These data were compared with the overall population in which 36% of patients were still receiving treatment and 33 patients across dose levels having died, 30 of whom died more than days from their last dose.

Among reported all-grade treatment-emergent AEs (TEAEs; ≥ 25%), the most common in the 60-mg and overall population were CRS (72% vs 57%, respectively), neutropenia (42% vs 37%), anemia (32% vs 29%), nausea (32% vs 29%), fatigue (27% vs 30%), diarrhea (28% vs 27%), and thrombocytopenia (25% vs 23%). Hematologic grade 3 or higher events included neutropenia (37% vs 34%,...
Pipeline Report

TABLE. Response Data With ABBV-383

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intention-to-treat population</th>
<th>60-mg dose in escalation and expansion cohorts</th>
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<tr>
<td></td>
<td>All dose levels (n = 122)</td>
<td>Triple-class refractory (n = 100)</td>
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<tr>
<td>ORR</td>
<td>57%</td>
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<td>sCR/CR</td>
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<td>VGPR</td>
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<td>PR</td>
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Responses were measured from the time of first dose administration. The ORR for all patients was 57% comprising a 29% CR/sCR rate, 14% PR rate, and 14% VGPR rate. The median time to first response was 0.7 months (range, 0.3-7.6) and the median time to first CR/sCR was 3.5 months (range, 1.4-20.1). Further, among the 69 respond- ers, the median DOR was not reached (95% CI, 12.9-NR) and the 6- and 12-month Kaplan-Meier estimates for response were 76.3% (95% CI, 63.2%-85.3%) and 67.2% (95% CI, 52.6%-78.2%), respectively (TABLE). For all triple-class refractory patients, the ORR was 51% with a 29% CR/sCR rate, an 11% PR rate, and an 11% VGPR rate. Among those with triple-class refractory disease to receive ABBV-383 at 60 mg, the ORR was 54%, with a 29% CR/sCR rate, a 10% VGPR rate, and a 15% VGPR rate. Of the 11 patients who were evaluable for minimal residual disease (MRD) with a CR or sCR, 8 were MRD negative (≤ 10^-5).

EXPANDED EFFICACY DATA WITH ABBV-383

“Encouraging preliminary antitumor activity in heavily pretreated patients with relapsed refractory multiple myeloma supports further clinical evaluation,” Voorhees said following a discussion with the myeloma program, and director of the unrelated donor transplantation programs for adults at UCSF Helen Diller Family Comprehensive Cancer Center, said. “[ABBV-383] had fixed dosing and was given at full dose for the first dose, so 1 hospitalization for 2 days. After that it was all outpatient administration.” Martin also associate director of UCSF’s myeloma program, and director of the unrelated donor transplantation programs for adults at UCSF Medical Center.

Other factors to consider, safety and efficacy, Martin drew from a comparison of other agents, such as REG-5458 and elranatamab, noting that ORRs are similar across the agents in the 60% to 70% range, with CRS being the lowest with ABBV-383 and REG-5458. Martin concluded by adding that future development should include a focus on fixed-duration therapy, with MRD serving a prognostic role for treatment-discontinuation decisions.

REFERENCES


secondary end point of response by International Myeloma Working Group 2016 criteria.

At baseline in the 60-mg cohort and the overall population combined, the median age was 68 years (range, 35-92) and most patients had an ECOG performance status of 1 (53% and 57%, respectively). The median number of prior lines of therapy was 5 (range, 3-15) and most patients were refractory to their last cancer therapy (85% and 87%, respectively), with most patients having triple-class refractory disease (83% and 82%). More patients in the 60-mg cohort had penta refractory disease (42%) vs the overall population (35%). Enrollment in the 60-mg dose-expansion cohort has been completed; however, an additional dose-expansion cohort (40 mg) has been added to the protocol and is open for enrollment.

NEXT STEPS FOR ABBV-383 IN MULTIPLE MYELOMA

In a discussion of the abstract, Thomas G. Martin, MD, noted that bispecifics are primed to play a role in the community setting compared with chimeric antigen receptor T-cell therapy. However, he noted that there are several areas where bispecifics can play a role in the myeloma space, but dosing is going to play a key role in the determination of which bispecifics move forward. “What we want is convenient dosing, every 3 to 4 weeks, which [ABBV-383] shows,” Martin, who is the clinical research director of hematologic malignancies at the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, said. “[ABBV-383] had fixed dosing and was given at full dose for the first dose, so 1 hospitalization for 2 days. After that it was all outpatient administration.” Martin also associate director of UCSF’s myeloma program, and director of the unrelated donor transplantation programs for adults at UCSF Medical Center.

Other factors to consider, safety and efficacy, Martin drew from a comparison of other agents, such as REG-5458 and elranatamab, noting that ORRs are similar across the agents in the 60% to 70% range, with CRS being the lowest with ABBV-383 and REG-5458. Martin concluded by adding that future development should include a focus on fixed-duration therapy, with MRD serving a prognostic role for treatment-discontinuation decisions.
To decrease the incidence of chemotherapy-induced myelosuppression in patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen

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THE FIRST AND ONLY PROACTIVE MULTILINEAGE MYELOPROTECTION THERAPY

In the Pivotal Study in 1st-line ES-SCLC, COSELA administered before an etoposide/carboplatin + atezolizumab (E/P/A) regimen resulted in:

- **REduced incidence and duration of severe neutropenia**
  Primary Endpoints: 1.9% vs 49.1% (P<0.0001) and 0 days vs 4 days (P<0.0001) with and without COSELA, respectively*

- **Numerically lowered incidence of grade 3/4 anemia and RBC transfusions**
  Secondary Endpoints: 19% vs 28% and 13% vs 21% with and without COSELA, respectively†

- **Reduced the incidence of grade 3/4 thrombocytopenia**
  Secondary Endpoint: 1.9% vs 37.7% with and without COSELA (P=0.0026)‡

- **Reduced rate of chemotherapy dose reductions**
  Secondary Endpoint: 2.1 vs 8.5 with and without COSELA (P=0.0196)§

INDICATION

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

*Multiplicity-adjusted P values. Adjusted relative risk (aRR) 0.038 (95% CI, 0.008, 0.195) and mean difference -3.6 (95% CI, -4.9, -2.3), respectively. Duration evaluated in Cycle 1.

†Adjusted relative risk (aRR) 0.683 (95% CI, 0.336, 1.310) and aRR 0.642 (95% CI, 0.294, 1.404). RBC transfusions measured on/after 5 weeks. Grade 3/4 anemia defined as Grade 3/4 decreased hemoglobin.

‡Raw one-sided P value not adjusted for multiplicity. aRR 0.053 (95% CI, 0.008, 0.356). Results for platelet endpoints including incidence of Grade 3/4 thrombocytopenia and platelet transfusions were not consistent across COSELA clinical trials; in studies 2 and 3, no difference in the incidence of Grade 3/4 thrombocytopenia AEs was observed between the COSELA and placebo groups.

§Raw one-sided P value not adjusted for multiplicity. Rate of all-cause dose reductions, events per 100 cycles. aRR 0.242 (95% CI, 0.079, 0.742).


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REVIEW MULTILINEAGE EFFICACY AT COSELA.COM
SPEAR THE TUMOR.
WHILE CHEMOTHERAPY TARGETS CANCER CELLS

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATION
• COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib.

WARNINGS AND PRECAUTIONS
Injection-Site Reactions, Including Phlebitis and Thrombophlebitis
• COSELA administration can cause injection-site reactions, including phlebitis and thrombophlebitis, which occurred in 56 (21%) of 272 patients receiving COSELA in clinical trials, including Grade 2 (10%) and Grade 3 (0.4%) adverse reactions. Monitor patients for signs and symptoms of injection-site reactions, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue COSELA. Injection-site reactions led to discontinuation of treatment in 3 (1%) of the 272 patients.

Acute Drug Hypersensitivity Reactions
• COSELA administration can cause acute drug hypersensitivity reactions, which occurred in 16 (6%) of 272 patients receiving COSELA in clinical trials, including Grade 2 reactions (2%). Monitor patients for signs and symptoms of acute drug hypersensitivity reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold COSELA until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue COSELA.

Interstitial Lung Disease/Pneumonitis
• Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, including COSELA, with which it occurred in 10 (0.4%) of 272 patients receiving COSELA in clinical trials. Monitor patients for pulmonary symptoms of ILD/pneumonitis. For recurrent moderate (Grade 2) ILD/pneumonitis, and severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

Embryo-Fetal Toxicity
• Based on its mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use an effective method of contraception during treatment with COSELA and for at least 3 weeks after the final dose.

ADVERSE REACTIONS
• The most common adverse reactions (≥10%) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia.

To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-G1TX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
This information is not comprehensive. Please see the Brief Summary of Prescribing Information on the adjacent page.
**Contraindications**

COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib, reactions that have included anaphylaxis. Refer to the prescribing information for these concomitant medications for assessing the benefit and risk of concomitant use.

**Warnings and Precautions**

**Cardiac Safety**

**Heart failure**

COSELA administration can cause increases in cardiac ventricular filling pressures, sinus tachycardia, and prolongation of the QT interval. In patients treated with COSELA, QTc intervals measured from =90% of patients receiving placebo increased by ≥6 milliseconds from baseline to a mean of 10.7 milliseconds at 1 hour for placebo and 12.1 milliseconds at 1 hour for patients receiving COSELA. QTc intervals measured from the start of the first dose of COSELA were ≥6 milliseconds and ≥12 milliseconds at 1 hour for placebo and COSELA, respectively. The median duration of treatment was 3 cycles in each treatment group.

**Renal failure**

COSELA can cause renal adverse reactions, including increases in serum creatinine, hypophosphatemia, and hyperkalemia. COSELA is contraindicated in patients with severe or life-threatening renal failure (creatinine clearance ≤15 mL/min).

**Hepatic impairment**

COSELA is contraindicated in patients with moderate or severe hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <1.5x ULN). AUC values in patients with moderate hepatic impairment were, on average, ~80% higher than in patients with normal hepatic function.

**Pregnancy**

COSELA can cause fetal harm when administered to a pregnant woman. Refer to the prescribing information for assessment of the benefit and risk of COSELA in pregnant women. COSELA is contraindicated in pregnant women.

**Lactation**

There is no information available on breastfeeding women treated with COSELA.

**Pediatric use**

Safety and effectiveness in pediatric patients have not been established.

**Elderly use**

In the pooled efficacy dataset from Studies 1, 2 and 3, 2% of 123 patients randomized to COSELA and 3% of 120 patients randomized to placebo ages ≥65 years old and 12% of patients ≥75 years old; 53% and 56% of patients ≥65 years of age and ≥75 years of age, respectively. No overall differences in safety or efficacy were observed between these two age groups.

**Hepatic Impairment**

COSELA is contraindicated in patients with moderate or severe hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <1.5x ULN). AUC values in patients with moderate hepatic impairment were, on average, ~80% higher than in patients with normal hepatic function.

**Nonclinical Toxicology**

**Carcinogenesis**

No studies have been performed in humans to evaluate the effects of COSELA on fertility in either sex.

COSELA can cause fetal harm when administered to pregnant women (see Warnings and Precautions (5.3) and Dosage and Administration (2.2)).

**Patent Counseling Information**

Inform patients of the ages and symptoms of injection-site reactions, including phlebitis and thrombophlebitis. Advise patients to contact their healthcare provider immediately for signs of infusion-site reactions or deep vein thrombosis.

**Hypersensitivity**

Refer to the prescribing information for assessing the benefit and risk of concomitant use.

**Drug Interactions**

Refer to the prescribing information for assessing the benefit and risk of concomitant use.

**Table 4: Potentially Significant Drug Interactions with COSELA**

Reactions and symptoms may recur when the same or higher incidence than in patients receiving placebo was hypophosphatemia.

**Table 3: Adverse Reactions Reported in ≥5% Patients with SCLC Receiving COSELA (with ≥2 Higher Incidence Compared to COSELA Compared to Placebo)**

**Table 2: Recommended Adverse Reactions**

**Table 1: Adverse Reactions by Body System**

**Table 3: Adverse Events (All Grades)**

**Table 2: AE Clustered Together by Body System**

**Table 1: Incidence of Adverse Reactions**

**Table 3: AE Clustered for Common Body System””
Understanding pCR's Role in Early-Stage TNBC Opens Doors for Tailored Treatment

by KRISTI ROSA

NEW OPPORTUNITIES TO IMPROVE

the treatment of patients with early-stage triple-negative breast cancer (TNBC) stem from understanding the prognostic link between pathologic complete response (pCR) and survival outcomes, according to Hope S. Rugo, MD, FASCO. The next step on the road map of progress in the disease will be to focus on identifying therapeutic approaches that are directed to biologic subsets.

“We have made some remarkable progress in the treatment for early-stage TNBC. We know that pCR is highly prognostic for longer-term outcomes [such as] event-free survival [EFS] and distant recurrence-free survival [DRFS],” Rugo said in a presentation during the 21st Annual International Congress on the Future of Breast Cancer® West. “...We can use this to capitalize on understanding how tumors respond on an individual basis and hopefully, try to provide therapy that is appropriate for each patient’s cancer.”

In her talk, Rugo, who is a professor of medicine and director of Breast Oncology and Clinical Trials Education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, discussed key lessons learned in the neoadjuvant treatment of TNBC, including optimal chemotherapy backbone, leveraging of immunotherapy, and novel combinations under exploration. As research efforts shift to personalized care, Rugo discussed how pCR and the predictive value of residual cancer burden (RCB) scoring are being leveraged as pivotal end points.

pCR: LESSONS LEARNED

Although it was known that pCR is a prognostic biomarker for long-term outcomes, investigators in the phase 2 I-SPY2 trial (NCT01042379) set out to understand the strength of this association with EFS and DRFS in subpopulations of patients with high-risk, operable breast cancer who received standard treatment with 1 or more novel therapies.

Three-year outcomes from the trial showed that achievement of a pCR following neoadjuvant therapy was linked with a reduction in recurrence rate of approximately 80%, irrespective of disease subtype and/or treatment regimen. Of the 950 participants, 34.7% achieved a pCR to treatment; the 3-year EFS and DRFS rates for those who experienced a pCR were 95%. Moreover, the HRs for pCR vs non-pCR were 0.19 (95% CI, 0.12-0.31) and 0.21 (95% CI, 0.13-0.34) for EFS and DRFS, respectively.

Hope S. Rugo, MD, FASCO

“Subsequently, published data [looked] at RCB score [and showed] that the amount of cancer that [the patient] has at the time of surgery—not just having none vs having some—has a big impact on DRFS and EFS over time,” Rugo explained. This knowledge can help clinicians to understand how individual tumors respond and thus select the optimal therapeutic option for each patient.

NEOADJUVANT PLATINUM: WHAT DO THE DATA SHOW?

Leveraging pCR as a marker for clinical benefit, investigators sought to establish the optimal chemotherapy backbones for patients with early-stage disease.

For example, the randomized, double-blind, placebo-controlled, phase 3 BrightNess trial (NCT02032277) paved the way for the regimen of paclitaxel and carboplatin regimen to be used in future studies of neoadjuvant chemotherapy, including the evaluation of the addition of immunotherapy.

“[BrightNess was] the largest trial to look specifically at what the addition of platinum does for pCR,” Rugo said. Of the 634 patients with TNBC enrolled, 316 received paclitaxel plus carboplatin and the PARP inhibitor veliparib (ABT-888), 160 received paclitaxel plus carboplatin, and 158 were given paclitaxel alone.

Data showed that those who received paclitaxel plus carboplatin alone experienced the highest pCR, at 58% vs 53% with paclitaxel/carboplatin and veliparib (P = .357) and 31% with paclitaxel alone (P < .0001). Among patients who were RCB class 0 or 1, the pCRs achieved in those who received paclitaxel plus carboplatin (n = 140) were 70% vs 68% in those who...
received paclitaxel/carboplatin and the PARP inhibitor (n = 268; P = .739) and 47% in those who received paclitaxel alone (n = 125; P < .0001).

“We saw that the addition of platinum to standard weekly paclitaxel, with all patients receiving AC [adriamycin/cyclophosphamide] after the combination chemotherapy and then going to surgery, resulted in a markedly higher pCR rate,” Rugo noted. “The addition of veliparib did not improve pCR further than the addition of carboplatin.”

Rugo added that an important component of the trial was understanding how to manage the toxicity of adding carboplatin to paclitaxel. Giving carboplatin on a weekly cadence improved the completion rate of anthracycline-based therapy following treatment with the doublet.

A post hoc analysis of the trial, which looked at EFS with paclitaxel plus carboplatin vs paclitaxel alone, showed that the HR was 0.57 (95% CI, 0.36-0.91; P = .02).4

“These are the best data that we have, suggesting that adding carboplatin to a paclitaxel-based backbone not only improved pCR but [had] an improvement in EFS with a long 4.5-year follow-up; this is more than adequate for TNBC,” Rugo said. “It led to the idea that adding platinum would improve outcomes for the majority of patients who had at least stage III TNBC in the neoadjuvant setting.”

Moreover, several trials have examined if the addition of a platinum agent to a taxane-based backbone could serve as an alternative for anthracyclines. The WSG-ADAPT-TN trial (NCT01815242) evaluated neoadjuvant nab-paclitaxel (Abraxane) plus carboplatin (n = 146) vs nab-paclitaxel plus gemcitabine (n = 178) in patients with TNBC. The pCR rates with these regimens were 45.9% and 28.7%, respectively (P < .001).5

“The trial clearly demonstrated that nab-paclitaxel and carboplatin was the optimal chemotherapy regimen if you eliminated anthracyclines in the neoadjuvant setting, with pCR as the end point,” Rugo noted.

USING PCR/RCB TO LEVERAGE CHECKPOINT INHIBITORS

Checkpoint inhibition has become a part of standard care for patients who have at least stage II TNBC, according to Rugo. The rationale for combining checkpoint inhibitors with chemotherapy is based on the idea that chemotherapy results in tumor lysis and antigen shedding, which enhances host immune response and upregulates PD-L1 expression.

The phase 3 KEYNOTE-522 trial (NCT03036488) enrolled patients with newly diagnosed stage II or III TNBC (n = 1174) and randomly assigned them 2:1 to receive neoadjuvant treatment with 4 cycles of pembrolizumab (Keytruda) at 200 mg every 3 weeks plus paclitaxel and carboplatin (n = 784), or placebo every 3 weeks plus paclitaxel/carboplatin (n = 390).

The primary end point was pCR at the time of surgery and EFS in the intention-to-treat population. “I think this is a model for future neoadjuvant-style trials, as the trial was powered for both a pCR end point, as well as an EFS end point, so you would not have to do a subsequent trial to understand the outcome on EFS,” Rugo noted.

Data from the first interim analysis showed that among the first 602 patients who were randomly assigned, 64.8% (95% CI, 59%-69.5%) of those who received pembrolizumab plus chemotherapy achieved a pCR vs 51.2% (95% CI, 44.1%-58.3%) with chemotherapy alone (P < .001).4 The EFS rates in the pembrolizumab and chemotherapy-alone arms were 91.3% (95% CI, 88.8%-93.3%) and 85.3% (95% CI, 80.3%-89.1%), respectively (HR, 0.63; 95% CI, 0.43-0.93).

The phase 3 IMpassion031 trial (NCT03197935) also enrolled those with previously untreated, stage II to III TNBC. Participants were randomly assigned 1:1 to receive chemotherapy plus atezolizumab (Tecentriq) at 840 mg (n = 165) or placebo (n = 168) every 2 weeks prior to surgery. Patients continued to receive 1 year of atezolizumab and this portion of the trial was unblinded. At a median follow-up of 20.6 months (IQR, 8.7-24.9) in the chemoinmunotherapy arm, and 19.8 months (IQR, 8.1-24.5) in the chemotherapy-alone arm, pCR rates were 57.6% and 41.1%, respectively (P = .0044).7

“We learned something from these trials about the impact of immune markers on response. The benefit from immunotherapy, comparing the control arm with the arm receiving pembrolizumab or atezolizumab, was independent of PD-L1 status on the tumor,” Rugo said.

Moreover, a higher pCR rate was observed with the immunotherapy agents in those with PD-L1–positive disease vs those with negative status; as such, PD-L1 was found to be predictive of response to chemotherapy.

“We know that tumor-infiltrating lymphocytes and PD-L1 not only predict response to chemotherapy, but also overall outcome,” Rugo said. “We might be able to use [available] data in the future to try to individualize therapy for patients with early-stage TNBC.”

Taking a Closer Look at KEYNOTE-522

Updated data from the KEYNOTE-522 trial, recently published in the New England Journal of Medicine, showed a statistically significant improvement in EFS (HR, 0.63; 95% CI, 0.48-0.82; P = .00031) and DRFS (HR, 0.61; 95% CI, 0.46-0.82) in those who received pembrolizumab and chemotherapy vs chemotherapy alone.8

“Remember that patients received 1 year of treatment with a checkpoint inhibitor and those on placebo received 6 months of chemotherapy,” Rugo said. “The curve separated at [approximately] 12 months and stayed separated over time; this is highly statistically significant and very exciting data.”

Data from the trial supported the July 2021 FDA approval of pembrolizumab in patients with high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant therapy after surgery.9

Subgroup analyses revealed that patients who had node-positive or node-negative disease, and those who had stage II or III disease, all derived benefit from the addition of pembrolizumab to chemotherapy. “However, the amount of disease that you start therapy with determines the pCR rate, even outside of whether they receive a checkpoint inhibitor,” Rugo said.

Specifically, those with node-positive disease who received pembrolizumab/chemotherapy or chemotherapy alone had lower pCR rates (80.7% vs 71.5%, respectively) than those with node-negative disease (88.6% vs 82.2%, respectively).10,11 The same was true for disease stage; those with stage III disease who received pembrolizumab/chemotherapy or chemotherapy alone experienced lower pCR rates than those with stage II disease, at 71.8% and 62%, respectively, vs 88.6% and 81.7%, respectively.10,11

“We know that pCR is highly prognostic for longer-term outcomes, [such as] event-free survival and distant recurrence–free survival...We can use this to capitalize on understanding how tumors respond on an individual basis, and hopefully, try to provide therapy that is appropriate for each patient’s cancer.”

— HOPE S. RUGO, MD, FASCO
“Interestingly, [this observation] did not translate into a difference by node status or stage in terms of benefit of pembrolizumab; you see benefit regardless of stage,” Rugo said. “In some ways, you could argue that the patients who have the higher-stage disease with the worst outcome benefit the most, but we can cure even more patients with lower-stage, better-risk disease by adding the checkpoint inhibitor.”

When looking at EFS by pCR status, it was found that patients who achieved a pCR, irrespective of whether they had received pembrolizumab, experienced an “excellent” outcome, according to Rugo. Those who did not achieve a pCR did not experience a large benefit with the immunotherapy. “This brought up the question of whether we could create a frameshift in the amount of residual disease,” Rugo noted.

To this end, investigators leveraged data from the first 600 patients included in KEYNOTE-522 to examine RCB in terms of EFS benefit.12 Data showed that those with an RCB score of 0 experienced a good outcome, irrespective of whether they received pembrolizumab. Those with an RCB score of 1 had outcomes that “were a little worse, but still overall good for this patient population,” according to Rugo. Those with an RCB score of 3 had very poor outcomes, irrespective of whether they received immunotherapy.

Several additional trials are examining checkpoint inhibitors in the neoadjuvant setting including the phase 3 NeoTRIP trial (NCT02620280) of atezolizumab and the phase 2 GeparNuoVelo trial (NCT02850509) of durvalumab (Imfinzi). Notable studies examining immunotherapies in the adjuvant setting include the phase 3 IMpassion030 trial (NCT03498716) comparing atezolizumab in combination with adjuvant anthracycline/taxane-based chemotherapy vs chemotherapy alone in operable TNBC; the phase 3 A-BraVe trial (NCT02926196) examining adjuvant avelumab (Bavencio) in high-risk TNBC; and the phase 3 SWOG S1418/BR006 trial (NCT02954874) examining adjuvant pembrolizumab.

According to Rugo, efforts are being made to determine which patients need checkpoint inhibitors (FIGURE).

ALTERNATIVE NEOADJUVANT APPROACHES

In addition to immunotherapy, approaches using different classes of agents, such as antibody-drug conjugates (ADC), have begun to gain traction in early-stage TNBC.

The phase 2 NeoSTAR trial (NCT04230109) is examining neoadjuvant treatment with sacituzumab govanecan-hzzy (Trodelvy) in patients with localized TNBC.13 Of the 50 patients enrolled in the trial, 12 had stage I disease, 26 had stage II disease, and 11 had stage III disease. Moreover, 62% of patients were node negative, and 9 patients had germline BRCA positivity.

Study participants received sacituzumab govanecan at a starting dose of 10 mg/kg for 4 cycles on days 1 and 8 of each 21-day treatment cycle. Following those 4 cycles, patients with residual disease confirmed via biopsy had the option to receive additional neoadjuvant therapy per physician discretion.

Data from the trial, presented during the 2022 American Society of Clinical Oncology Annual Meeting, showed that the pCR rate achieved in the overall population was 30%. In patients with stage I, II, and III disease, these rates were 50%, 27%, and 18%, respectively. Moreover, the pCR rate with the ADC in those with BRCA-positive disease was 75%.

“They are now studying the same regimen in combination with pembrolizumab,” Rugo said. “There are a lot of data to suggest that giving ADCs with pembrolizumab may enhance the effect of the checkpoint inhibitors, so we will be interested to see those data, as well as others that are looking at ADCs in combination with checkpoint inhibitors in the neoadjuvant setting.”

Investigators of the single-arm phase 2 NeoPACT trial (NCT03639948) took another look at the efficacy of chemoinmunotherapy and employed a biomarker analysis to identify potential prognostic factors of pCR. The trial examined pembrolizumab in combination with docetaxel and carboplatin for 6 cycles in 109 evaluable patients with TNBC; notably, 88% of patients had stage II or III disease, Rugo said.

Data showed that the pCR achieved with this approach in those with stage III disease was 43%, “which is very good,” Rugo said.14 Those with stage I disease had a pCR rate of 69% and those with stage II disease had a pCR rate of 59%. Those who achieved a pCR experienced a 2-year EFS rate of 98%.

In the biomarker analysis, patients who had a high rate of stromal tumor–infiltrating lymphocytes of 30% or higher experienced a higher pCR than those with a lower rate below 30%, at 76% and 41%, respectively (odds ratio [OR], 4.66; 95% CI, 2.02-10.78; P < .001). Moreover, those with a high DNA damage immune response signature had a higher pCR than those who did not, at 71% and 46%, respectively (OR, 2.90; 95% CI, 1.20-7.00; P = .018).
CDK4/6 Inhibitors Could Fill Treatment Void for Patients With HR+/HER2- Early Breast Cancer

by KYLE DOHERTY

CDK4/6 INHIBITORS HAVE THE potential to fill an unmet need in the treatment of patients with early stage breast cancer, especially for those who develop primary resistance to endocrine therapy, according to a presentation by Joyce O’Shaughnessy, MD, at the 21st Annual International Congress on the Future of Breast Cancer East.1

“We still have a lot of work to do in hormone receptor-positive/HER2-negative breast cancer,” O’Shaughnessy, the Celebrating Women Chair in breast cancer research at Baylor University Medical Center in Dallas, Texas, said during the presentation. “We have the issue of primary endocrine therapy resistance. Some of those patients are chemotherapy sensitive, but some of them are [also] cross-resistant to chemotherapy. In the first couple years of being diagnosed with hormone receptor-positive/HER2-negative breast cancer, patients start recurring [despite] optimal single-agent endocrine therapy. In the first 2 to 3 years after a diagnosis of hormone receptor-positive/HER2-negative breast cancer, [there] are the highest annual odds of recurrence. Those are the patients with primary endocrine therapy-resistant disease that we do not have good tools for.”

CDK4/6 inhibitors palbociclib (Ibrance) and abemaciclib (Verzenio) have previously displayed striking data in the metastatic setting, explained O’Shaughnessy, who is also the director of the Breast Cancer Research Program at Texas Oncology and chair of breast cancer research for the US Oncology Network. Thus, investigators made it a priority to evaluate the agents in the adjuvant setting. The agents are similar, though abemaciclib inhibits significantly more kinases compared with palbociclib and can also be given continuously because it is not as myelosuppressive, she noted.

PALBOCICLIB IS NOT THE ANSWER FOR HR+/HER2- EARLY BREAST CANCER

The phase 3 PALLAS trial (NCT02513394) compared the efficacy of palbociclib plus adjuvant endocrine treatment with that of endocrine treatment alone among patients with stage II-III HR-positive/HER2-negative breast cancer. Eligible patients underwent prior surgery (with or without chemotherapy or radiotherapy), were within 12 months of their diagnosis, and were within 6 months of starting adjuvant endocrine treatment. Palbociclib was administered at a dose of 125 mg daily for 3 weeks on and 1 week off, plus standard endocrine therapy. Patients in the control group received standard endocrine therapy alone. The primary end point was invasive disease-free survival (iDFS).2

At a median follow-up of 31 months, no significant difference was observed in terms of 4-year iDFS. The 4-year iDFS was 84.2% and 84.5% in the combination and monotherapy arms, respectively (HR, 0.96; 95% CI, 0.81-1.14; P = .65).

In the phase 3 PENETROPE-B trial (NCT01864746), patients with hormone receptor-positive/HER2-negative breast cancer with residual disease received palbociclib plus endocrine therapy or placebo plus endocrine therapy following neoadjuvant chemotherapy and surgery. Like PALLAS, at a median follow-up of 42.8 months, no significant difference in iDFS was reported between the 2 arms (HR, 0.93; 95% CI, 0.74-1.17; P = .525).3

“The curves have come together at 4 years,” O’Shaughnessy said. “There was this intriguing split in the curve early on, but it came back together. This raises the question, in a high-risk population, of whether a longer duration of therapy might have benefitted these patients.”

ABEMACICLIB SHOWS GREAT PROMISE

In the phase 3 monarchE trial (NCT03155997), patients with high-risk hormone receptor-positive/HER2-negative early breast cancer were randomly assigned 1:1 to received either abemaciclib plus standard-of-care endocrine therapy or endocrine therapy alone. Patients were divided into cohorts based on high-risk clinical pathological features (cohort 1) or high-risk Ki-67 scores (cohort 2). Patients in the investigational arm were treated with abemaciclib 150 mg twice daily continuously without a break.4

At a median follow-up of 27 months, patients in the intent-to-treat population who received abemaciclib experienced a 30.4% reduction in the risk of experiencing an iDFS event compared with those who received endocrine therapy alone (HR, 0.696; 95% CI, 0.588-0.823; P = .0001). There was also an absolute difference in the 3-year iDFS rates of 5.4% that favored the abemaciclib arm. The distant recurrence-free survival risk was reduced by 31.3% in abemaciclib arm (HR, 0.687; 95% CI, 0.571-0.826; P < .0001), with an absolute difference of 4.2% between the 3-year rates.

Additionally, among patients in the intent-to-treat population who received neoadjuvant chemotherapy, the 2-year iDFS rate also favored the abemaciclib arm compared with the endocrine therapy arm at 87.2% and 80.6%, respectively (HR, 0.61; 95% CI, 0.47-0.80; log-rank P < .001). The 2-year distant disease-free survival rates were 89.5% and 82.8%, respectively (HR, 0.61; 95% CI, 0.46-0.81; log-rank P < .001).

Similarly, patients in the intent-to-treat population with high Ki-67 (≥ 20%) experienced a 33.7% reduction in the risk of developing an iDFS event when they were treated with abemaciclib (HR, 0.663; 95% CI, 0.524-0.839; P = .0006). The absolute difference in 3-year iDFS rates between the arms was 6.0%.

Notably, patients treated with abemaciclib in cohort 1 who also had high Ki-67, experienced a 37.4% reduction in the risk of developing an iDFS event (HR, 0.626; 95% CI, 0.488-0.803; P = .0002). The absolute difference in 3-year iDFS rates between the arms was 7.1%.

“The FDA wanted to take a look at the highest-risk population,” O’Shaughnessy said. “The patients [in cohort 2] were a protocol amendment and started enrolling a bit after cohort 1, so the follow-up was not as great. The [patients in cohort 1 who were enrolled from the beginning] were a very high anatomic risk group, and the FDA wanted to look at those that were highly proliferative in addition. Basically, [we found] that the higher the risk, the higher the impact of abemaciclib. This is the group that led to the FDA [approval] for adjuvant abemaciclib.”

High Ki-67 is prognostic of a worse outcome, but it is not predictive of abemaciclib benefit, O’Shaughnessy explained. Patients derived a benefit from treatment with abemaciclib regardless of Ki-67 score.

In October 2021, the FDA approved abemaciclib for the adjuvant treatment of adult patients with hormone receptor-positive/HER2-negative, node-positive early breast cancer at a risk of recurrence and a Ki-67 score of at least 20%.5

THE FUTURE OF CDK4/6 INHIBITORS

CDK4/6 inhibitors are currently under investigation in patients with hormone receptor-positive/HER2-negative early breast cancer in multiple ongoing clinical trials. The phase 3 ADAPTlate trial (NCT04565054) is evaluating delayed extended abemaciclib in patients with high-risk disease. Adjuvant abemaciclib is also being
A BALANCE OF DATA

1L aRCC treatment that OFFERS A BALANCE OF DATA:
superior OS,* safety & tolerability, patient-reported quality of life1-6†‡

* 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

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, hematemesis, 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\textsuperscript{1,3,4}
(median follow-up time of 18.1 months; range: 10.6-30.6 months)

**MEDIAN PFS WAS DOUBLED\textsuperscript{*}\textit{**}

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**ORR WAS DOUBLED\textsuperscript{*}\textit{**}

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\textsuperscript{*}PFS and ORR were assessed by BICR.\textsuperscript{1}

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**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.\textsuperscript{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 anti-diarrheals 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=35) 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.

---

**ADVERSE REACTIONS**

**Osteonecrosis of the Jaw (ONJ):** ONJ occurred in 8% of CABOMETYX patients. Monitor patients for symptoms of ONJ. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX after at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

**Impaired Wound Healing:** Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

**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.
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-3TIL, 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, 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.

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

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


For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

Learn more at CABOMETYXhcp.com
5.9 Protonuria
Protonuria was observed in 8% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX for at least 5 days until improvement to Grade 1 or below, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in 11% of patients treated with CABOMETYX, ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, tooth extraction, gingival or parulis, jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

5.11 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of cerebrovascular narrowing, occurred in 4% of patients receiving CABOMETYX, including Grade 3 in 0.4% of patients.

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

5.14 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.

5.15  Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. CABOMETYX administration to pregnant animals during organogenesis resulted in embryo-fetal toxicity at doses below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise preganant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 1 month after the last dose.

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, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect experiences in patients with advanced renal cell carcinoma treated with either CABOMETYX (n=322) or sorafenib (490 patients) with RCC enrolled in randomized, active-controlled trials (CASOSUN, MECTOR). 467 patients with RCC enrolled in randomized, placebo-controlled trial (CELESTIAL) with nivolumab. 123 patients with RCC enrolled in a randomized, active-controlled trial (COMPARE) and 418 patients with RCC enrolled in a randomized, active-controlled trial (CHEKOMATE-IREN).

Based on clinical trials of another drug, an adverse reaction in 1% or more of patients with treated with CABOMETYX in MECTOR was: Peripheral Edema, Grade 3–4 occurred in 4% of patients treated with CABOMETYX.

Other clinically important adverse reactions (all grades) that were reported in ≥10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (8%), proteinuria (1%), osteosarcoma of the jaw (1%), and hepatitis cholestatic (1%).
Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pulmonary embolism, urinary tract infection, and hypertension. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 5% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either CABOMETYX or nivolumab occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs separately.

The most common adverse reactions reported in ≥25% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, myalgia, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abnormally painful cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥15% of Patients receiving CABOMETYX and Nivolumab-CHEKOMATE-BER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX and Nivolumab (%)</th>
<th>Nivolumab (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>Grades 1-4</td>
<td>Grades 3-4</td>
<td>Grades 1-4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>64</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Abdominal Painb</td>
<td>22</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Dyspepiaca</td>
<td>15</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Dysphoniab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>33</td>
<td>39</td>
<td>30</td>
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<tr>
<td>Muscle paini</td>
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<td>39</td>
<td>9</td>
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<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>35</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>77</td>
<td>24</td>
<td>46</td>
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<tr>
<td>Increased LDH</td>
<td>84</td>
<td>2.8</td>
<td>37</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>39</td>
<td>4.7</td>
<td>37</td>
</tr>
<tr>
<td>Increased AST</td>
<td>84</td>
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<td>37</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>39</td>
<td>4.7</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 5. Laboratory Values Worsening from Baseline Occurring in >20% of Patients receiving CABOMETYX and Nivolumab-CHEKOMATE-BER

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX and Nivolumab (%)</th>
<th>Nivolumab (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>Grades 1-4</td>
<td>Grades 3-4</td>
<td>Grades 1-4</td>
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<tr>
<td>Chemistry</td>
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</tr>
<tr>
<td>Increased ALT</td>
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<td>6.8</td>
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<tr>
<td>Increased AST</td>
<td>72</td>
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<td>37</td>
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<tr>
<td>Increased LDH</td>
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<td>8.9</td>
<td>48</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>54</td>
<td>1.9</td>
<td>34</td>
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<tr>
<td>Increased ALT</td>
<td>79</td>
<td>6.8</td>
<td>39</td>
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<td>48</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>54</td>
<td>1.9</td>
<td>34</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>79</td>
<td>6.8</td>
<td>39</td>
</tr>
<tr>
<td>Increased AST</td>
<td>72</td>
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<td>37</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>78</td>
<td>8.9</td>
<td>48</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>54</td>
<td>1.9</td>
<td>34</td>
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Table 6. Adverse Reactions Occurring in ≥15% of Patients-Treated Patients in CHEKOMATE-BER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (%)</th>
<th>Nivolumab (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>Grades 1-4</td>
<td>Grades 3-4</td>
<td>Grades 1-4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>64</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Abdominal Painb</td>
<td>22</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Dyspepa</td>
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<td>28</td>
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<tr>
<td>General</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>8</td>
<td>50</td>
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<tr>
<td>Dysphonia</td>
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<td>Increased ALT</td>
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<tr>
<td>Increased ALT</td>
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<td>Increased ALT</td>
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<td>Nervous System</td>
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<tr>
<td>Respiratory, Thoric, and Mediastinal</td>
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<tr>
<td>Gynecomastia</td>
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<td>Myalgia</td>
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<tr>
<td>Metabolism and Nutrition</td>
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<td>Respiratory System</td>
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<tr>
<td>Myalgia</td>
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<td>7</td>
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<tr>
<td>Infection and infestations</td>
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<tr>
<td>Upper respiratory tract infection</td>
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</table>

CHECKOMATE-BER

The safety of CABOMETYX with nivolumab was evaluated in CHECKOMATE-BER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or suntinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.
Table 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-3111

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (N=125)</th>
<th>Placebo (N=237)</th>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (27)</td>
<td>24 (10)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (9)</td>
<td>9 (4)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (7)</td>
<td>3 (1)</td>
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<tr>
<td>Stomatitis</td>
<td>3 (2)</td>
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<td>Diarrhea and vomiting</td>
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<td>Vomiting</td>
<td>1 (1)</td>
<td>1 (1)</td>
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<tr>
<td>General</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (15)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>21 (17)</td>
<td>6 (2.5)</td>
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<td>Increased ALT</td>
<td>21 (17)</td>
<td>5 (2.2)</td>
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<td>Increased bilirubin</td>
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<td>1 (0.5)</td>
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<tr>
<td>Hypoalbuminemia</td>
<td>12 (10)</td>
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<tr>
<td>Neutrophils decreased</td>
<td>25 (20)</td>
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<tr>
<td>Leukocytes decreased</td>
<td>38 (30)</td>
<td>8 (3.4)</td>
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<tr>
<td>Platelets decreased</td>
<td>31 (25)</td>
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<td>Lymphocytes decreased</td>
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<td>Renal and Urinary</td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>Hypertension</td>
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<td>2 (0.8)</td>
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Table 9. Laboratory Abnormalities Occurring in ≥25% of CABOMETYX-Treated Patients in COSMIC-3111

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (N=125)</th>
<th>Placebo (N=237)</th>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LDH increased</td>
<td>90 (72)</td>
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</tr>
<tr>
<td>AST increased</td>
<td>70 (56)</td>
<td>8 (3.4)</td>
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<td>Hypocholesterolemia</td>
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<td>AIP increased</td>
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<tr>
<td>Hypophosphatemia</td>
<td>15 (12)</td>
<td>2 (0.8)</td>
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7 DRUG INTERACTIONS
7.1 Effects of Other Drugs on CABOMETYX

Co-administration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib by up to 25-fold. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

7.2 Special Populations

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no sufficient data in pregnant women to inform the drug-associated risk. In animal development and reproduction studies, administration of CABOMETYX to pregnant rats and rabbits caused decreased fetal body weight and delayed fetal osseous development. In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in reduced fetal development and fetal abnormalities.

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in reduced fetal development and fetal abnormalities. In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in reduced fetal development and fetal abnormalities.

8.2 Lactation

There is no information regarding the presence of cabozantinib or its metabolites in human milk. It is not known whether CABOMETYX is excreted in human milk, or their effects on the breastfed child or milk production. Due to the potential for serious adverse reactions in breastfeeding children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 females and Males of Reproductive Potential

Pregnancy

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception

Advise CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Males

Advise males of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is not recommended for patients aged 12 years and older.

8.5 Geriatric Use

In CHECKMATE-9ER, 41% of patients treated with CABOMETYX were age 65 years or older, and 8% were 75 years or older. In CELESTIAL, 49% of patients treated with CABOMETYX were age 65 years or older, and 15% were 75 years or older. In COSMIC-311, 50% of 126 patients treated with CABOMETYX were age 65 years or older, and 15% were 75 years or older. No overall difference in safety or effectiveness was observed between these patients and younger patients.

Due to the lack of randomized CABOMETYX administration with placebo in CHECKMATE-9ER, 11% were 65 years or older and 5% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment by a 10% reduction in the recommended dosing (Child-Pugh C). Since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

8.8 OVERDOSAGE

One case of overdose was reported following administration of another formulation of cabozantinib: a patient inadvertently took twice the intended dose for 8 days. The patient suffered Grade 3 memory impairment. Grade 3 mental status changes. Grade 3 cognitive disturbance. Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

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

Hormonal: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs and symptoms of unusual bleeding or bruising.

Per sistential and fatal bleeding: Advise patients that CABOMETYX can cause persistent and fatal bleeding.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately notify their healthcare provider if they experience any change in vision.

Hypocalcemia: Advise patients to take their calcium supplements as directed.

Hypertension: Advise patients to contact their healthcare provider for further advice on how to manage hypertension.

Hypothyroidism: Advise patients to contact their healthcare provider for further advice on how to manage hypothyroidism.

Hypokalemia: Advise patients to contact their healthcare provider for further advice on how to manage hypokalemia.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing.

Oncogenesis of the jaw: Advise patients regarding good oral hygiene practices.

Adrenal insufficiency: Advise the patient to contact their healthcare provider for further advice on how to manage hypothyroidism.

Impaired wound healing: Advise patients to contact their healthcare provider for further advice on how to manage hypothyroidism.

Hypokalemia: Advise patients to contact their healthcare provider for further advice on how to manage hypothyroidism.

18.1 PATIENT COUNSELING INFORMATION

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating. This brief summary is based on the CABOMETYX Prescribing Information.
examined in high-risk patients in the phase 3 POETIC-A trial (NCT04584853). Finally, the phase 2 CARABELA trial (NCT04293393) is investigating neoadjuvant abemaciclib plus endocrine therapy among patients with intermediate or high-risk disease.¹

Neoadjuvant treatment with CDK4/6 inhibitors such as abemaciclib has the potential for clinical utility, O’Shaughnessy noted. In the phase 2 neoMONARCH trial (NCT02441946), 66.1% of patients who received abemaciclib plus anastrozole experienced complete cell cycle arrest (Ki-67 < 2.7%) at 2 weeks compared with 58.8% and 14.8% among patients who received abemaciclib monotherapy and anastrozole monotherapy, respectively.² Similarly, in the phase 2 PALLET trial (NCT02296801), 90% of patients who received palbociclib plus letrozole achieved complete cell cycle arrest at week 14 compared with 59% who received letrozole monotherapy (P < .001).²

“If you have a patient who you know is going to be a good candidate [for the monarchE regimen] but they are not surgical candidates at that moment, and they are either not chemotherapy candidates or the biology of [their] disease is such that you do not feel they will benefit from chemotherapy, I have been starting the monarchE treatment with an aromatase inhibitor plus abemaciclib preoperatively to downsize, get them to surgery, and then continue the adjuvant therapy,” O’Shaughnessy said. ■

REFERENCES


Intrinsic Tumor Subtyping Is Key to Breast Cancer Treatment

by JASON HARRIS

The Importance of Identifying the Genomic Intrinsic Subtype of Breast Cancer

The importance of identifying the intrinsic tumor subtype of breast cancer cannot be overstated, Charles M. Perou, PhD, said during the 21st Annual International Congress on the Future of Breast Cancer® (IBC) East. Intrinsic subtype can predict treatment response and prognosis, particularly for basal-like subtype tumors within non-triple-negative breast cancers (TNBCs).

“I will continue to make the argument that knowing a tumor subtype is important, particularly when you find a basal-like cancer in an area where you don’t think you’re going to find it,” Perou said. “Within hormone receptor-positive, HER2-negative [disease there is a] potential benefit of CDK4/6 inhibitors varying by subtype. For [luminal] A and B, there is a benefit and for basal-like, there’s not a benefit. In HER2-enriched [disease], the kind of CDK4/6 [inhibitor] may matter. We’ll see.”

Perou is the May Goldman Shaw Distinguished Professor of Molecular Oncology, codirector of the Computational Medicine Program, faculty director of the University of North Carolina (UNC) Lineberger Bioinformatics Group, codirector of UNC Lineberger Breast Cancer Research Program, and a professor in the department of genetics at the UNC Lineberger Comprehensive Cancer Center in Durham. He is also the 2019 Giants of Cancer Care® award winner for cancer diagnostics and delivered the Giants lecture at IBC East.

Perou said the luminal A and B (LumA and LumB) subtypes appear in up to 70% of breast cancers, including most estrogen receptor- and progesterone receptor-positive tumors. These subtypes are prognostic for outcomes and associated with a treatment benefit from endocrine therapy and chemotherapy.

The basal-like subtype is present in 10% to 15% of tumors, but it is seen in up to 75% of TNBCs. The overwhelming majority of TNBCs are TP53 deficient. They are typically highly proliferative and tend to be immune infiltrated.

“When we’re studying TNBC, we’re really studying basal-like breast cancers,” Perou said. “We really have to study and attack the biology of basal-like breast cancers,” Perou said. “We really have to study and attack the biology of basal-like breast cancers, which includes an association with BRCA1 mutation status.”

Finally, there is the HER2-enriched subtype, which is present in 10% to 15% of tumors. This subtype is defined in part by amplification of the HER2 region on 17q11-12. More than 70% of tumors in this subtype are TP53-mutated, and the subtype is predictive of benefit for HER2-targeting agents and combinations. “Almost all HER2-enriched tumors, but not all, are HER2 amplified and as you’ll see, certainly not all HER2-amplified tumors fall into this expression subtype.”

Conventional wisdom says TNBCs are highly heterogeneous. However, Perou argued that TNBCs are the most homogeneous group, whereas HER2-positive tumors are the most heterogeneous.

“They have all the subtypes present, and all of them present at a decent frequency. And that’s going to matter,” he said.

He cited data from the phase 3 MONALEESA-2 (NCT01958021), MONALEESA-3 (NCT02422615), and MONALEESA-7 (NCT02278120) trials to illustrate the prognostic relationship of PAM50-based subtypes with progression-free survival (PFS) and risk of disease progression by subtype and treatment. Patients were treated with endocrine therapy and ribociclib (Kisqali) for hormone receptor-positive, HER2-negative advanced breast cancer.³

Subtype distribution was 46.7% for LumA, 24.0% for LumB, 14.0% for normal like, 12.7% for HER2-enriched, and 2.6% for basal-like. Investigators profiled 1160 tumors, with 672 patients assigned to ribociclib and 488 assigned to placebo. Distribution of subtypes was generally consistent across treatment arms and trials.

Prat et al found that associations between subtypes and PFS were statistically significant in both arms (P < .001). All subtypes except basal-like (HR, 1.15; P = .77) derived significant PFS benefit with ribociclib: HER2 enhanced (HR, 0.39; P < .0001), LumB (HR, 0.52; P < .0001), LumA (HR, 0.63; P = .0007), and normal-like (HR, 0.47; P = .0005).

“Typically, basal-like in the HER2 enriched [subtype], particularly HER2 enriched in the absence of HER2 targeting, is the worst player,” Perou said. “Now, the interesting part of this study was when [they] looked at the benefit. These are randomized trials with and without the CDK4/6 inhibitor, and in this case, you can see there’s a benefit of the CDK4/6 inhibitor in luminal A, [luminal] B, and HER2-enriched [subtypes], but not in basal-like.”

Similarly, findings from the phase 3 CALGB 40601 trial (NCT00770809) showed that dual HER2-targeting agents induced a benefit for relapse-free survival (RFS) and pathologic complete response (pCR) compared with single targeting. Investigators assessed trastuzumab (Herceptin) plus lapatinib (Tykerb; n = 118),
trastuzumab alone (n = 120), or lapatinib alone (n = 67) in women with untreated stage II and III HER2-positive breast cancer.2

At a median follow-up of 83 months, patients in the combination arm had significantly better RFS compared with trastuzumab monotherapy (HR, 0.32; 95% CI, 0.14-0.71; P = .005). There was no difference between the monotherapy arms.

Seven-year OS rates were 84% for lapatinib, 88% for trastuzumab, and 96% for the combination. OS was significantly higher in the combination arm than in the trastuzumab arm (HR, 0.34; 95% CI, 0.12-0.94; P = .037).

Eighty-nine (61%) of 146 HER2-enriched patients had a pCR in the breast compared with 29 (25%) of 118 non-HER2-enriched patients (odds ratio, 3.8; 95% CI, 2.23-6.72; P < .001). Investigators identified significant RFS differences among the different subtypes. LumA tumors had the lowest pCR rate (14.3%) but carried the best RFS outcome, with no events recorded after 7 years of follow-up. In contrast, HER2-enriched patients had the highest pCR rate but a significantly worse RFS outcome, with 30 (20.5%) of 146 RFS events recorded.

CONFLICTING FINDINGS IN TNBC

In long-term results from the phase 2 CALGB 40603 trial (NCT00861705), a 2 x 2 randomized study, investigators determined that adding carboplatin and/or bevacizumab (Avastin) to standard neoadjuvant chemotherapy improved pCR rates compared with chemotherapy alone in TNBC.3 However, data published in 2019 and 2022 did not show a subsequent benefit for event-free survival (EFS).4,5

Perou said that finding was both disappointing and in contrast to results from the phase 3 BrighTness trial (NCT02032277). Those data showed that carboplatin plus veliparib (ABT-888) with paclitaxel improved both pCR and EFS compared with paclitaxel alone (HR, 0.63; 95% CI, 0.43-0.92; P = 0.02) at a median follow-up of 4.5 years.6

“Time permitting, I could spend 30 minutes discussing possible hypotheses about these,” which was different [from] what we saw [in] BrighTness,” he said. “We’re actually in the midst of doing a combined analysis of BrighTness and [CALGB 40603] with genomics and clinical data, so hopefully we can learn something about that discrepant result between those 2 studies.”

Investigators analyzed more than 850 clinical and genomic features for association with outcomes in CALGB 40603. Only 27 were associated with both. Twenty-four of the features associated with both pCR and EFS reflected the tumor’s immune microenvironment including the presence of a variety of immune effector cells such as T and B lymphocytes and natural killer cells. Investigators also determined that higher mRNA expression levels of immune checkpoint genes, including tumor-infiltrating lymphocytes (TILs), PD-L1, and PD-L1 were associated with improvements in both pCR and EFS.

However, Perou noted that investigators performed multivariate analysis, adding TILs, age, pCR status, and stage to the base model to predict EFS. TILs were not a predictor for EFS, but the addition of CD8 T-cell signature was. “I believe that the gene expression signatures of the immune features are better predictors of event-free survival than our than our TILs,” Perou said. “I’m going to claim also they’re more objective and more reproducible. Amongst triple negatives, there’s Pam50 subtypes, there’s the Vanderbilt subtypes, there’s the MD Anderson subtypes. Long story short, I’m going to argue they didn’t really matter.”

REFERENCES


Waks on the Continued Evaluation of Immunotherapy in HER2+ Breast Cancer

Adrienne G. Waks, MD, discusses the data from the phase 3 IMpassion050 trial (NCT03726879) and the phase 2 KATE2 trial (NCT02924883) that support the exploration of immune checkpoint blockade in HER2-positive breast cancer.

WATCH NOW: bit.ly/3AXjYEb

Bardia on the Need for Oral SERDs in ESR1-Mutant ER+ Breast Cancer

Patients with metastatic estrogen receptor–positive breast can develop ESR1 mutations and are resistant to aromatase inhibitors, explains Aditya Bardia, MD, MPH, highlighting the importance of oral selective estrogen receptors (SERDs) is important for this population.

WATCH NOW: bit.ly/3PVSFi5

Pegram on the Evolving Treatment Landscape in HER2+ Breast Cancer

Mark Pegram, MD, discusses how practice-changing data and new agents have reshaped the HER2-positive breast cancer space; however, the influx of treatments presents challenges for clinicians to stay abreast of varying toxicity profiles and other unique features.

WATCH NOW: bit.ly/3uGPeE
Escalation or De-escalation Strategies Require Careful Consideration in HER2+ Breast Cancer

by KYLE DOHERTY

MULTIPLE PATIENT CHARACTERISTICS, including risk level and tumor size, may play a role in determining whether patients with HER2-positive breast cancer are candidates for escalated or de-escalated HER2-directed therapy, according to a presentation by Sara A. Hurvitz, MD, during the 21st Annual International Congress on the Future of Breast Cancer West.1

“Outcomes for [patients with] HER2-positive breast cancer have substantially improved with the advent of HER2-directed therapy,” Hurvitz, associate professor at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA), and director of the Breast Cancer Clinical Trials Program at UCLA. “We can tell our patients [that] HER2-positive disease is associated with some of the best outcomes now. With that said, we must decide which patients are eligible for escalated therapy vs de-escalated therapy. Almost all patients will receive some form of systemic therapy if they have HER2-positive disease.”

CLINICIAN DISCRETION IS KEY IN THERAPY ESCALATION

Regarding treatment escalation for patients with HER2-positive breast cancer that is high risk, Hurvitz noted that current evidence-based strategies point to different approaches, according to characteristics including response to therapy. For example, she explained that results from the phase 3 KATHERINE trial (NCT01772472) advocate for adjuvant ado-trastuzumab emtansine (T-DM1; Kadcyla) for all patients with residual disease.

Escalating therapy may be an option for those who are at high risk of recurrence or progression, but other factors may play into the appropriate patient selection. Hurvitz said that findings from the phase 3 ExteNET trial (NCT00878709) support the use of adjuvant neratinib (Nerlynx) in select patients with residual disease, adding that she would recommend this approach in patients who are hormone receptor positive and high risk, such as those with high residual nodal burden. However, she noted that this recommendation must be balanced against the potential toxicities of the regimen.

In ExteNET, patients with HER2-positive early stage breast cancer were randomly assigned 1:1 to receive either neratinib 240 mg daily for 1 year or placebo. All patients had previously been treated with trastuzumab (Herceptin). The primary end point of the trial was invasive disease-free survival (iDFS), and there was a 5-year extended follow-up for iDFS and overall survival (OS).2 “Keep in mind, this study did not allow patients who had received pertuzumab [Perjeta] or T-DM1,” Hurvitz said. “[Therefore] the relative benefits or absolute benefits of neratinib in patients who had received those agents is not entirely clear.”

Findings from the trial showed that the 5-year iDFS rates were 90.2% and 87.7% in the neratinib and placebo arms, respectively (HR, 0.73; 95% CI, 0.57-0.92; \(P = .0008\)). A minimal benefit in OS was observed between the 2 arms (HR, 0.95; 95% CI, 0.74-1.21; \(P = .6914\)).

When broken down by hormone receptor status, a clearer benefit in terms of iDFS was observed in the neratinib arm. Patients with hormone receptor-positive disease experienced a 5-year iDFS rate of 91.2% when treated with neratinib compared with 86.8% in the placebo arm (HR, 0.60; 95% CI, 0.43-0.83). Comparatively, among patients with hormone receptor-negative disease, the 5-year iDFS rates were 88.9% and 88.8%, respectively (HR, 0.95; 95% CI, 0.66-1.35).

Additionally, in a subgroup analysis, a greater iDFS benefit was reported among patients with hormone receptor-positive disease and residual disease and were less than a year removed from adjuvant treatment with trastuzumab. In this subgroup, patients who were treated with neratinib experienced a 5-year iDFS rate of 85.0% compared with 77.6% among patients who received placebo (HR, 0.60; 95% CI, 0.33-1.07). In terms of OS, the 8-year rates were 91.3% and 82.2%, respectively (HR, 0.47; 95% CI, 0.22-0.92).

Ongoing studies of novel approaches to treating high-risk breast disease include the phase 3 CompassHER2 RD trial (NCT04457596) and ASTEFAVIA (NCT04873362) trials.

DE-ESCALATION APPROACH DEPENDS ON TUMOR SIZE, OTHER ASPECTS

In terms of therapy de-escalation in the neoadjuvant setting, Hurvitz clarified that systemic therapy is still necessary for all patients with small (< 1.5 cm) HER2-positive tumors. She also suggested that neoadjuvant therapy should be considered for patients with tumors 1.5 cm or greater and that, in this setting, pathologic response is prognostic and informs adjuvant therapy decision-making. “One of the benefits of the neoadjuvant setting is it gives us an opportunity to feel really comfortable about omitting anthracyclines from our therapy, because we can see [whether] the treatment we have chosen has worked,” Hurvitz said.

In the phase 2 TRYPHAENA study (NCT00976989), investigators evaluated 3 neoadjuvant treatment regimens among patients with locally advanced, inflammatory, or early stage HER2-positive breast cancer. Patients were randomly assigned 1:1:1 to receive pertuzumab plus trastuzumab with 5-fluorouracil/epirubicin/cyclophosphamide (FEC) for cycles 1 to 3 and docetaxel for cycles 4 to 6; FEC for cycles 1 to 3 followed by pertuzumab plus trastuzumab with docetaxel for cycles 4 to 6 (THP); or 6 cycles of pertuzumab plus trastuzumab with docetaxel and carboplatin (TCH).2

Findings from the trial showed that the TCHP approach and the FEC to THP strategy led to similar outcomes in terms of pathological complete response (pCR). Hurvitz said the longer-term disease-free survival and progression-free survival results trended toward the TCHP arm, meaning it was safer from a cardiac perspective.

Another trial, the phase 2 neoCARH study (NCT03140553), compared the efficacy of epirubicin/cyclophosphamide followed by docetaxel/trastuzumab (EC-T) with that of docetaxel/carboplatin/trastuzumab (TCH). The study compared the combinations in the neoadjuvant setting among patients with HER2-positive breast cancer under the single HER2 blockade.4 Patients treated with TCH displayed a superior pCR rate compared with those who received EC-T: 37.3% (95% CI, 25.8%-50.0%) vs 55.9% (95% CI, 43.3%-67.9%), respectively ( \(P = .032\)). Hurvitz also noted that the TCH regimen produced better outcomes in terms of adverse effects.

Hurvitz then emphasized that the phase 3 TRAIN-2 trial (NCT01996267) was the study that solidified the nonanthracycline approach in the neoadjuvant setting. In this trial, patients with stage II to III HER2-positive breast cancer were randomly assigned 1:1 to receive FEC plus paclitaxel or paclitaxel, trastuzumab, and carboplatin plus trastuzumab.5

“The pCR rates were virtually equivalent in the 2 treatment arms, but more patients were able to complete the full year of trastuzumab in the nonanthracycline arm,” Hurvitz said. “The longer-term follow-up looks as good with the nonanthracycline [regimen] as the anthracycline-based regimen.”

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

Sara A. Hurvitz, MD
IS MYELOFIBROSIS TREATMENT ILL-FITTED TO PATIENT NEEDS?

Not all options are sufficient for all patients — which leaves them with less than optimal outcomes.¹ New approaches must be pursued to manage a fuller range of signs and symptoms in myelofibrosis.

TO LEARN MORE, VISIT MYELOFIBROSISINSIGHTS.COM

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