BRCA Rules Leave Patients Behind

ALSO IN THIS ISSUE

PEER EXCHANGE
HEMATOLOGIC MALIGNANCIES
New Follicular Lymphoma Approach

OncoPathways®
IMMUNOTHERAPY
IDO Field Shows Signs of Life

ESMO 2019 HIGHLIGHTS
BREAST CANCER
CDK4/6 Evidence Builds

GI CANCER
Novel Agent for GIST

GU CANCERS
PARP Gains in mCRPC

PRECISION MEDICINE IN ONCOLOGY
LUNG CANCER
A Niche for TRK Inhibitors

MEMORIAL SLOAN KETTERING CANCER CENTER
Hepatic Infusion Can Convert CRC Liver Metastases to Operable State
BY NANCY KEMENY, MD; MICHAEL I. D’ANGELICA, MD, FACS; & JASHODEEP DATTA, MD
OXIDATIVE STRESS

The presence of phosphorylated STAT3 in a tumor may indicate

Learn more about ROS generation in cancer cells

inhibit multiple oncogenic pathways and modify immune responses.

Boston Biomedical, Inc. is a leading developer of next-generation cancer therapeutics designed to

References:

©2019 Boston Biomedical, Inc. All rights reserved. Boston Biomedical is a registered trademark of Sumitomo Dainippon Pharma Co., Ltd. PM-NPS-0877 (6/2019)
All human cells maintain a redox balance between reactive oxygen species (ROS) and antioxidants, such as NQO1, to resist oxidative stress.\textsuperscript{1,2} The optimal redox balance differs between cells and determines their specific “redox signature,” which can have downstream effects on potent oncogenic signaling pathways, including STAT3.\textsuperscript{1,3,4}

Research suggests that a subset of cancer cells, including some cancer stem cells, possess a distinct redox signature that may make them susceptible to approaches that generate cytotoxic levels of ROS.\textsuperscript{3,4} These cells signal to other cells in the tumor microenvironment and promote the phosphorylation of STAT3. The presence of phosphorylated STAT3 in a tumor may indicate this redox signature and favorability to ROS-generating intervention.\textsuperscript{3}

Learn more about ROS generation in cancer cells at www.bostonbiomedical.com
Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 84.
New BRCA screening guidelines from the United States Preventive Services Task Force are an improvement over previous recommendations but are still too conservative to meet the needs of individuals at risk of developing certain cancers and of patients diagnosed with malignancies associated with the mutation, according to oncology experts.

**BRCA Rules Leave Patients Behind**

**12** Tips for Talking With Patients: “Mother Question” and Sleep Test
By Maurie Markman, MD

**OVARIAN CANCER**

**32** Niraparib Improves PFS as Frontline Maintenance in Ovarian Cancer

**34** Trametinib Demonstrates Efficacy in Recurrent, Low-Grade Ovarian Cancer

**36** Frontline Veliparib Regimen Shows Intriguing PFS Findings

**PROSTATE CANCER**

**37** Apalutamide Is Linked to OS Benefit in Nonmetastatic CRPC

**39** Olaparib Doubles rPFS in Heavily Pretreated mCRPC

**40** Cabazitaxel Emerges as Third-Line Standard in Metastatic CRPC

**GI CANCERS**

**46** Abemaciclib/Fulvestrant Improves Survival in HR+ Advanced Breast Cancer

**47** CDK4/6 Activity Extends to HER2+ Breast Cancer Setting

**48** Ribociclib/Fulvestrant Combo Improves OS in Advanced HR+ Breast Cancer

**HEAD AND NECK CANCERS**

**52** Positive ORR Findings for RET Inhibitor in Thyroid Cancer Set the Stage for FDA Submission

**LUNG CANCER**

**53** Durvalumab Combo Improves QOL, Reduces New Lesions in Small Cell Lung Cancer

**CLINICAL TRIAL IN FOCUS**

**56** Investigators Link Novel Biomarker to Therapy in DLBCL Trial

**CLINICAL PERSPECTIVES**

**62** Rising Incidence of Fatty Liver Disease Holds Implications for Trends in HCC

**64** Novel Induction Regimens Boost Outcomes in Myeloma

**Surgery Retains Important Role in Evolving RCC Paradigm**
Well Begun, But Half Done

IT’S A DICEY MATTER to come out with a new recommendation on care in oncology. Sometimes the guideline will be accepted as a no-brainer and be embraced by the physician community, or it may excite controversy, despite the best of intentions, which was the case recently when the US Preventive Services Task Force (USPSTF) updated its 2013 recommendation on risk assessment, genetic counseling, and genetic testing for BRCA-related cancer.

The USPSTF did an evidence-based analysis, taking a conservative approach, and advised that primary care clinicians use appropriate risk assessment tools to assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer, or who have an ancestry associated with BRCA1/2 mutations.

The oncology community has for the most part embraced the update as a big step forward. The update specifically states that personal cancer history and ancestry, such as Ashkenazi Jewish roots, are risk factors warranting assessment, which the 2013 guideline did not.

However, oncology experts have noted that the scope of the update gives scant attention to some populations at risk for BRCA1/2 mutation–driven cancers. One such group is African American women, who are twice as likely as white women to develop triple-negative breast cancer,1 which is associated with BRCA1 mutation carrier status. Critics said this omission may, in fact, magnify disparities in care.

In its defense, the USPSTF said it arrived at its recommendations on breast, ovarian, tubal, and peritoneal cancers because this was where net benefit was demonstrated by available evidence. Oncologists contend that the USPSTF should have turned to other sources of information or expertise to enlarge the scope of the guideline.

The USPSTF did not review evidence for testing and counseling men at risk for BRCA1 mutation–driven cancer. This is another significant gap in the recommendations, critics said, because BRCA1/2 mutations are present in 6% of men who have metastatic prostate cancer.2

Screening and risk assessment tools also deserve more guideline attention, because the multiple tools on the market can produce different results for the same patient. For example, the Referral Screening Tool includes Ashkenazi Jewish ancestry, but the Ontario Family History Assessment Tool does not. Further, tests may yield different recommendations for treatment.

The issue here is that, even when guidelines on testing are followed, physician training is of paramount importance for appropriate intervention. Critics say guidelines should emphasize the need for more training.

As our cover story notes, the USPSTF guideline on BRCA1/2 mutation–driven cancer is a careful step forward onto solid ground, but much work remains to be done in tying up the loose ends.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES


CONTRAINDICATIONS

DARZALEX® (daratumumab) is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Infusion Reactions – DARZALEX® can cause severe and/or serious infusion reactions, including anaphylactic reactions. In clinical trials, approximately half of all patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and were Grade 1-2. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema, and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Intermittent infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting infusion.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference With Serological Testing – Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

Neutropenia and Thrombocytopenia – DARZALEX® may increase neutropenia and/or thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to the manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils and/or platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors for neutropenia or transfusions for thrombocytopenia.

Interference With Determination of Complete Response – Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Adverse Reactions – The most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions, neutropenia, thrombocytopenia, fatigue, asthenia, nausea, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia and upper respiratory tract infection.

DARZALEX® in combination with lenalidomide and dexamethasone (DRd): The most frequent (≥20%) adverse reactions for newly diagnosed or relapsed refractory patients were, respectively, infusion reactions (41%, 48%), diarrhea (57%, 43%), nausea (32%, 24%), fatigue (40%, 35%), pyrexia (23%, 20%), upper respiratory tract infection (52%, 65%), muscle spasms (29%, 26%), dyspnea (32%, 21%), and cough (30%, 30%). In newly diagnosed patients, constipation (41%), peripheral edema (41%), back pain (34%), asthenia (32%), bronchitis (29%), pneumonia (26%), decreased appetite (22%), and peripheral sensory neuropathy (24%) were also reported. In newly diagnosed patients, serious adverse reactions (≥2% compared to Rd) were dehydration (2%), bronchitis (4%), and pneumonia (15%), and treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were leukopenia (35%), neutropenia (56%), and lymphopenia (52%). In relapsed/refractory patients, serious adverse reactions (≥2% compared to Rd) were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%), and pyrexia (3%), and treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were neutropenia (53%) and lymphopenia (52%).
Now Approved:
For your adult patients with newly diagnosed, transplant-ineligible multiple myeloma

DARZALEX® (daratumumab) + Rd*

REDEFINING APPROACHES IN EARLY LINES OF MULTIPLE MYELOMA

For a strong start to their treatment journey
*Rd=lenalidomide (R) + dexamethasone (d).

Longer PFS and deep responses¹
- Median PFS not reached with DARZALEX® + Rd after median follow-up of 28 months⁠† vs 31.9 months for Rd alone¹ ²
- 44% reduction in the risk of disease progression or death vs Rd alone (HR=0.56; 95% CI, 0.43-0.73; P<0.0001)
- 93% ORR with 48% CR or better (≥CR) vs 81% ORR and 25% ≥CR with Rd alone

Demonstrated safety profile when combined with Rd in the MAIA study²
- The most frequent (≥20%) adverse reactions were infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea, and cough
- Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

Study Design: MAIA, an open-label, randomized, phase 3 study, compared treatment with DARZALEX® + lenalidomide + dexamethasone (DRd) (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible MM. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.

CI= confidence interval; CR=complete response; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; ORR=overall response rate; PFS=progression-free survival.
†Range: 0.0–41.4.

DARZALEX® is a CD38-directed cytolytic antibody indicated for the treatment of adult patients with multiple myeloma:
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy


Learn more at darzalexhcp.com

For a strong start to their treatment journey

© Janssen Biotech, Inc. 2019 09/19 cp-79227v4
**DARZALEX® (daratumumab) injection, for intravenous use**

**INDICATIONS AND USAGE**

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

**CONTRAINDICATIONS**

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation [see Warnings and Precautions and Adverse Reactions].

**WARNINGS AND PRECAUTIONS**

**Infusion Reactions:** DARZALEX can cause severe and/or serious infusion reactions including anaphylactic reactions. In clinical trials, approximately half of all patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and were Grade 1-2 [see Adverse Reactions].

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusions or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as flushing, itching, nausea, rash and urticaria. Common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension [see Adverse Reactions].

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening event [Grade 4] reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion [see Dosage and Administration (2.1) in Full Prescribing Information].

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions [see Dosage and Administration (2.2) in Full Prescribing Information]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

**Intolerance with Serological Testing:** Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion.

Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References]. The determination of a patient’s ABO and Rh blood type are not impacted [see References].

**Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.**

**Neutropenia:** DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow neutrophil recovery. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

**Thrombocytopenia:** DARZALEX may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with platelet transfusions.

**Intolerance with Determination of Complete Response:** Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein [see Drug Interactions]. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

**ADVERSE REACTIONS**

The following clinically significant adverse reactions are also described elsewhere in the labeling:

- Infusion reactions [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

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

**Key:** D=daratumumab, Rd=lenalidomide-dexamethasone.

**Table 1: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the DRd arm in MAIA**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>Rd (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td><strong>Infusion reactions</strong></td>
<td>41</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>52</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>29</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>26</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>14</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>34</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>29</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>6</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

- Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.
- Generalized edema, Gravitational edema, Edema, Periarticular edema, Peripheral swelling.
- Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Diphtheria, Malignant neoplasm of respiratory tract.
- Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection.
- Bronchitis, Bronchiolitis, Bronchitis viral, Respiratory syncytial viral bronchiolitis, Tracheobronchitis.
- Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis.
- Cough, Productive cough.
- Blood pressure increased, Hypertension.

**Laboratory abnormalities worsening during treatment from baseline listed in Table 2.**

**Table 2: Treatment-emergent hematologic laboratory abnormalities in MAIA**

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>DRd (N=364) %</th>
<th>Rd (N=365) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>64</td>
<td>41</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

**Combination Treatment with Bortezomib, Melphalan and Prednisone**

Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 14.3 months (range: 0 to 25.8 months) for the daratumumab, bortezomib, melphalan and prednisone (D-VMP) group, and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in a Phase 3 active-controlled study ALYCYONE. The most frequent adverse reactions (≥20%) with at least 5% greater frequency in the D-VMP arm were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least a 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).
Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% for each). At least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 1%), edema peripheral (DRd 1% vs Rd 0%), dyspnea (DRd 1% vs Rd 0%), cough (DRd 8% vs Rd 6%), and muscle spasms (DRd 1% vs Rd 0%).

The overall incidence of serious adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, bronchitis, laryngitis, viral infection, and pulmonary sepsis.

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.

### Table 3: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the D-VMP arm in ALCYONE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>D-VMP (N=346)</th>
<th>VMP (N=354)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders</td>
<td>Edema peripheral</td>
<td>21 1 0 14 1 0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>48 5 0 28 3 0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>16 0 0 8 &lt; 1 0 0</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>10 4 1 &lt; 1 3 2 0</td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, V=melphalan-prednisone

Released/Refractory Multiple Myeloma

### Table 4: Treatment-emergent hematologic laboratory abnormalities in ALCYONE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>47 18 0 50 21 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>88 27 11 88 26 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>86 34 10 83 44 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>85 46 12 83 34 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, V=melphalan-prednisone

### Table 5: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the DRd arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
<td>46 5 0 0 0 0</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6: Treatment-emergent hematologic laboratory abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Grade</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>52 13 0 57 19 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73 7 6 67 10 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>92 36 17 87 32 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>95 42 10 87 6 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone

Combination Treatment with Bortezomib and Dexamethasone

Adverse reactions described in Table 7 reflect exposure to DARZALEX for a median treatment duration of 6.5 months (range: 0 to 14.8 months) in the daratumumab-bortezomib-dexamethasone (DVd) group and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib-dexamethasone group (Vd) in a Phase 3 active-controlled study CASTOR. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough, and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group.

Adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

### Table 7: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the DVd arm CASTOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
<td>45 9 0 0 0 0</td>
<td></td>
</tr>
</tbody>
</table>

### Table 8: Treatment-emergent hematologic laboratory abnormalities in CASTOR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>48 13 0 56 14 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>90 28 18 85 22 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 12 3 40 5 &lt; 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>89 41 7 81 24 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Vd=bortezomib-dexamethasone

Laboratory abnormalities worsening during treatment from baseline are listed in Table 8.
DARZALEX® (daratumumab) injection

Combination Treatment with Pomalidomide and Dexamethasone

Adverse reactions described in Table 9 reflect exposure to DARZALEX, pomalidomide and dexamethasone (DPd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months) in EQUULEUS. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, back pain, arthralgia, dizziness, insomnia, cough and dyspnea. The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations in 13% of patients.

Table 9: Adverse reactions with incidence ≥10% reported in EQUULEUS

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DPd (N=156) %</th>
<th>N=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>38 3 0</td>
<td>38 3 0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>33 0 0</td>
<td>33 0 0</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>30 0 0</td>
<td>30 0 0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>21 2 0</td>
<td>21 2 0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>50 10 0</td>
<td>50 10 0</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>25 1 0</td>
<td>25 1 0</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>20 0 0</td>
<td>20 0 0</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>17 0 0</td>
<td>17 0 0</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>15 0 0</td>
<td>15 0 0</td>
</tr>
<tr>
<td></td>
<td>Non-cardiac chest pain</td>
<td>15 0 0</td>
<td>15 0 0</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>11 0 0</td>
<td>11 0 0</td>
</tr>
<tr>
<td></td>
<td>Infecions and infestations</td>
<td>Upper respiratory tract infection</td>
<td>50 4 1</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>15 8 2</td>
<td>15 8 2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalemia</td>
<td>16 3 0</td>
<td>16 3 0</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>13 5 1</td>
<td>13 5 1</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>11 0 0</td>
<td>11 0 0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td>26 1 0</td>
<td>26 1 0</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>25 6 0</td>
<td>25 6 0</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>22 2 0</td>
<td>22 2 0</td>
</tr>
<tr>
<td></td>
<td>Pain in extremity</td>
<td>15 0 0</td>
<td>15 0 0</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td>13 4 0</td>
<td>13 4 0</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal chest pain</td>
<td>13 2 0</td>
<td>13 2 0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>21 2 0</td>
<td>21 2 0</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>19 3 0</td>
<td>19 3 0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>17 0 0</td>
<td>17 0 0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>23 2 0</td>
<td>23 2 0</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>13 0 0</td>
<td>13 0 0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>43 1 0</td>
<td>43 1 0</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>33 6 1</td>
<td>33 6 1</td>
</tr>
<tr>
<td></td>
<td>Nasal congestion</td>
<td>16 0 0</td>
<td>16 0 0</td>
</tr>
</tbody>
</table>

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

* Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.

Infections and infestations:

- Upper respiratory tract infection: Includes bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

In EQUULEUS, patients receiving daratumumab combination treatment (n=97) were administered the Daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion reactions was 40% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 4% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion reaction at Week 2 or subsequent infusions. The median time to onset of a reaction was 1.5 hours (range: 0.1 to 72.8 hours). The incidence of infusion modification due to reactions was 37%. Median durations of 16 mg/kg infusions for the 1st week, 2nd week and subsequent infusions were approximately 7, 4, and 3 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

In EQUULEUS, patients receiving daratumumab combination treatment (n=97) were administered the Daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Herpes Zoster Virus Reactivation: Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpetic zoster was reported in 3% of patients. In the combination therapy studies, herpetic zoster was reported in 2–5% of patients receiving DARZALEX.

Infusion Reactions: In clinical trials (monotherapy and combination treatments; N=1530) the incidence of any grade infusion reactions was 40% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 4% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion reaction at Week 2 or subsequent infusions. The median time to onset of a reaction was 1.5 hours (range: 0.1 to 72.8 hours). The incidence of infusion modification due to reactions was 37%. Median durations of 16 mg/kg infusions for the 1st week, 2nd week and subsequent infusions were approximately 7, 4, and 3 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

In EQUULEUS, patients receiving daratumumab combination treatment (n=97) were administered the Daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Hepatitis B Virus Reactivation: Hepatitis B virus reactivation has been reported in less than 1% of patients treated with DARZALEX as monotherapy or combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 749 combination therapy patients, tested positive for HBsAg at baseline.

Immunogenicity: As with all therapeutic proteins, there is the potential for immunogenicity. The incidence of antibodies to daratumumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 749 combination therapy patients, tested positive for antibodies to daratumumab at baseline.
positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of DARZALEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests: Interference with Indirect Antiglobulin Tests (Indirect Coombs Test): Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests: Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations (see Clinical Considerations). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

Lactation: Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breastfed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential: Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

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

Geriatric Use: Of the 1530 patients that received DARZALEX at the recommended dose, 48% were 65 to 74 years of age and 22% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients (see Clinical Studies (14) in Full Prescribing Information).

REFERENCES


PATIENT COUNSELING INFORMATION

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

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

• Itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing (see Warnings and Precautions and Adverse Reactions).

Neutropenia

• Advise patients that if they have a fever, they should contact their healthcare professional (see Warnings and Precautions and Adverse Reactions).

Thrombocytopenia

• Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding (see Warnings and Precautions and Adverse Reactions).

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion (see Warnings and Precautions and Drug Interactions).

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response (see Warnings and Precautions and Drug Interactions).

Hepatitis B Virus (HBV) Reactivation:

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again (see Adverse Reactions).

Manufactured by: Janssen Biotech, Inc. U.S. License Number 1894 © 2015 Janssen Pharmaceutical Companies Horsham, PA 19044 cp-60865v3
NOT SURPRISINGLY, as a longtime practicing oncologist specializing in gynecological cancer, I have noticed that certain themes and questions about individualized, scientifically unanswerable dilemmas often recur when I talk to patients and families about treatment. I have found that unique approaches appear to be helpful at these times.

Perhaps most common is a rather specific question posed by patients or family members regardless of their socioeconomic background, educational or professional attainments, or degree of knowledge of the specific clinical setting being confronted. The query is what I call “the mother question” and is most frequently asked in clinical circumstances that are difficult, complex, or both. This request is likely raised at the end of a consultation when we typically discuss multiple options, such as diagnostic tests, therapies, and clinical trial availability, as well as increasingly large volumes of information from the internet brought to the meeting by the patient or a family member. Some of this information comes from recognizable and respected organizations within the medical/oncology community, but much is from websites that would surely fail to satisfy this description.

The statement is a general variation of the following: “Doctor, I appreciate based on what you have said that you cannot recommend one course of action as the absolute best approach in this specific clinical situation. But I must ask you, what would you recommend if you were advising your own mother?”

It is essentially always the mother and not another family member, likely because of the truly unique and irreplaceable role she plays in everyone’s life. Of course, with experience, I have learned to respond by acknowledging the importance of the question and expressing my genuine belief that my opinion would be the same if I were recommending care for my mother.

A second common issue in consultations has been the dilemma regarding the necessary decision by a patient to either undergo or not undergo a specific intervention or diagnostic testing strategy. For example, in my practice, a significant issue has been whether a woman with advanced ovarian cancer who just completed her primary treatment of surgery and chemotherapy should continue obtaining routine (often monthly) cancer antigen (CA) 125 blood tests to “monitor the course of the disease.” A well-established diagnostic test, CA 125 plays a rather unique role in active ovarian cancer management; during therapy, serum antigen level can be usefully predictive of the overall degree of disease response, stability, or progression.

Unfortunately, definitive clinical utility of routine monitoring of the serum CA 125 level in women who have achieved a clinically defined complete response, which includes “normalization” of this blood-based biomarker, has not been established. In fact, a somewhat controversial randomized trial that examined this question failed to reveal a population-based improvement in overall survival associated with a once-every-3-months monitoring strategy.¹

"With experience, I have learned to respond by acknowledging the importance of the question and expressing my genuine belief that my opinion would be the same if I were recommending care for my mother."
FROM THE EDITOR

This study offered no proof of the value of routine measurement of CA 125 in the follow-up of patients with ovarian cancer who obtain a complete response after first-line treatment, nor did it provide evidence that would help a specific woman with ovarian cancer decide whether to continue a routine monitoring strategy—likely to have been regularly employed during her previous treatment program—or discontinue having the blood test and simply wait to see if symptoms or other signs of the illness return.

In discussing this situation with a patient and, commonly, her family, I will describe a scenario that will be referred to as "the sleep test." The patient is asked whether she will likely have less difficulty sleeping due to anxiety associated with not obtaining the test result and possibly constantly worrying what was happening to her serum value, versus being more concerned with knowing the laboratory value result each time the blood biomarker is obtained. There is surely no single "correct answer" to this question; rather, there is only the psychological and emotional impact on an individual patient resulting from applying the particular diagnostic paradigm. And, of course, the expression "sleep test" is employed solely to focus the attention of the patient on the impact (relatively positive or negative) the decision will have on her well-being.

It is not difficult to think of other clinical settings in which a process similar to this sleep test may have value. Individuals at a defined high risk of developing breast cancer and who may benefit from the administration of a noncytotoxic pharmaceutical agent (tamoxifen, raloxifene, or aromatase inhibitors) will have to decide if the associated adverse events (AEs) justify the potential benefits of treatment. In choosing, the patient must recognize that she may not derive any benefit from the medication.

Will she sleep better at night knowing she is doing something established in evidence-based clinical trials to be of benefit to a population of women similar to her, or will the potential for low-grade AEs and absence of knowledge of the value of such therapy for her negatively affect her perceived overall quality of life?

It is relevant to note that there has been no intent in this commentary to ignore that certain testing strategies and potential therapeutic interventions considered by individual patients and their families will not necessarily have the highest level of scientific evidence supporting their clinical utility, and there may be valid objections to their use due to cost. These concerns are legitimate. It is also important to recognize the major importance of these often complex, very difficult, and highly personal decisions and how they will affect individual patients.

REFERENCES

Niraparib (Zejula) is now approved for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status.

HRD is defined by a BRCA mutation that is deleterious or suspected of being deleterious or by genomic instability in patients with disease progression ≥6 months after response to the most recent platinum-based chemotherapy.

The approval is based on results from the single-arm, phase II QUADRA study (NCT02354586), which showed that niraparib elicited an overall response rate (ORR) of 24% (95% CI, 16%-34%). The ORR comprised partial responses in the primary efficacy population of patients who had HRD and received ≥3 prior lines of therapy (n = 98). The estimated median duration of response was 8.3 months (95% CI, 6.5-not estimable).

Along with the niraparib decision, the FDA also approved the Myriad myChoice companion diagnostic assay to determine HRD status in patients with advanced ovarian cancer who are may be eligible to receive niraparib.

In QUADRA, investigators evaluated the safety and efficacy of niraparib in 463 adult patients with metastatic, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients received the agent at 300 mg daily.

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

Two MET-Targeting Therapies Land Breakthrough Designations
Tepotinib and capmatinib, 2 investigational therapies that target MET exon 14 skipping (METex14) alterations in patients with nonsmall cell lung cancer (NSCLC), are among the latest novel therapies for which the FDA has granted breakthrough therapy designation.

MET alterations are present in 3% to 5% of patients with NSCLC and are associated with aggressive tumor behavior and poor prognosis. Currently, no FDA-approved treatments specifically target MET alterations.

Tepotinib
Tepotinib is being evaluated among patients with the mutation who have progressed on prior platinum-based chemotherapy, based on findings from the ongoing phase II VISION trial (NCT002864992).

The agent demonstrated an objective response rate (ORR) of 50.0%, as assessed by independent review committee (IRC) and an investigator-assessed ORR of 55.3% in patients with METex14-altered NSCLC. For patients identified to have METex14 alterations via tissue biopsy, the IRC- and investigator-assessed ORRs were 45.1% and 54.9%, respectively.

The VISION study is comprised of 2 groups: cohort A enrolled patients with METex14 mutations and cohort B included those with MET amplification. In both groups, tepotinib was administered at 500 mg once daily in a 21-day cycle.

Capmatinib
Capmatinib has earned a breakthrough therapy designation for the first-line treatment of patients with METex14–mutated NSCLC. The decision is based on primary findings from the phase II GEOMETRY mono-1 study (NCT02414139), in which capmatinib showed a 67.9% objective response rate (95% CI, 47.6%-84.1%) by independent review (IR) in treatment-naïve patients with METex14-altered NSCLC.

Data from cohorts 4 and 5b were presented at the 2019 American Society of Clinical Oncology Annual Meeting. Cohort 4 included pretreated patients with METex14 alterations in the second- or third-line setting (n = 69). Cohort 5b included included treatment-naïve patients (n = 28).

The median duration of response by IR was 9.72 months in pretreated patients and 11.14 months in those who received the agent up front. The median progression-free survival was 5.42 months in the pretreated group and 9.69 months for those treated in the frontline setting.

Capmatinib previously received both orphan drug and breakthrough therapy designations for patients with METex14 mutation–positive metastatic NSCLC following platinum-based chemotherapy.

FDA ORs Earlier Use of Romiplostim
The FDA has approved a supplemental biologics license application for the prescribing information of romiplostim (Nplate) to include new data that show sustained platelet responses in adults with immune thrombocytopenia (ITP). Romiplostim is indicated for the treatment of adults with newly diagnosed ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

The decision, which supports earlier use of the agent in this patient population, is based on a phase II trial (NCT01143038) of 75 previously treated adults ≥6 months from their ITP diagnosis.

Patients had a median length of platelet response (≥50 x 10⁹/L) of 11 months (95% CI, 10-11) during the 12-month treatment period. First platelet response occurred at a median time of 2.1 weeks (95% CI, 1.1-3.0) from treatment initiation. Of the 75 total patients 70 (93%), had ≥1 platelet response.

Neratinib Label Receives Update for HER2+ Breast Cancer
The FDA has approved a labeling supplement for neratinib (Nerlynx) for the extended adjuvant treatment of patients with HER2-positive early-stage breast cancer.

The update includes safety information based on interim results of the phase II CONTROL trial (NCT02400476), which evaluated antidiarrheal prophylaxis or dose escalation in the reduction of neratinib-associated diarrhea. The study’s primary end point was incidence of grade ≥3 diarrhea.

Eligible patients received neratinib at 240 mg daily for 1 year and oral loperamide prophylaxis for 1 or 2 cycles. Investigators gave loperamide at ≤16 mg daily, as needed, following completion of loperamide prophylaxis (n = 137). Patients enrolled on the budesonide (n = 64) or colestipol (n = 120) cohorts received the respective agents for 1 cycle.

Findings showed that prophylactic treatment with loperamide and budesonide reduced the discontinuation rate of neratinib due to associated diarrhea to 11%. The rate was 18% for those who received loperamide alone.

Additional findings presented at the 2019 American Society of Clinical Oncology Annual Meeting demonstrated that adding budesonide or colestipol to loperamide does reduce the rate of neratinib discontinuation due to diarrhea, thereby permitting patients to receive the full 1-year dose.
GIST exhibits broad intra- and inter-tumor heterogeneity, with multiple mutations fueling resistance and progression. A novel approach to kinase inhibition against a broad spectrum of KIT and PDGFRα mutations may potentially transform treatment in GIST.

Nearly all patients with GIST will eventually develop clinical resistance to imatinib. GIST exhibits broad intra- and inter-tumor heterogeneity, with multiple mutations fueling resistance and progression. A novel approach to kinase inhibition against a broad spectrum of KIT and PDGFRα mutations may potentially transform treatment in GIST.

Could broader mutational coverage translate to sustained disease control?

Deciphera is committed to uncovering scientific insights around resistance and progression, in order to develop novel approaches for patients with GIST. Learn more at RethinkGIST.com.
FDA LABEL CHANGES

XGEVA (DENOSUMAB)
- Clinical Trials Experience updated
  - Atypical subtrochanteric and diaphyseal fracture
    - In the clinical trial program, atypical femoral fracture has been reported in patients treated with denosumab, and the risk increased with longer duration of treatment.
    - Events have occurred during treatment and after treatment was discontinued.
- Postmarketing Experience expanded
  - Lichenoid drug eruptions (eg, lichen planus–like reactions)
  - Alopecia

THALOMID (THALIDOMIDE)
- Warnings and Precautions updated
  - Severe cutaneous reactions
    - Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with thalidomide use.
    - DRESS may present with a cutaneous reaction, such as rash or exfoliative dermatitis, eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis.
    - These events can be fatal. Interrupt or discontinue thalidomide for grade 2 to 3 skin rash. Discontinue for grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions, and do not resume therapy.
  - Hypersensitivity
    - Hypersensitivity to thalidomide, including angioedema and anaphylactic reaction, has been reported.
    - Do not resume thalidomide after these events have been observed.
- Postmarketing Experience expanded
  - Immune system disorders
    - Hyperkalanemia and anaphylactic reaction has been reported.
  - Skin and appendages
    - Alopecia

MVASI (BEVACIZUMAB-AWWB)
- Warnings and Precautions expanded
  - Additions and revisions to 12 sections
  - Congestive heart failure (CHF) added
    - Bevacizumab-awwb is not indicated for use with anthracycline-based chemotherapy.
    - The incidence of grade ≥3 left ventricular dysfunction was 1% in patients receiving bevacizumab-awwb compared with 0.6% in those receiving chemotherapy alone.
    - Among patients who received prior anthracycline treatment, the rate of CHF was 4.0% for patients receiving bevacizumab-awwb with chemotherapy compared with 0.6% for those receiving chemotherapy alone.
    - In previously untreated patients with a hematologic malignancy, the incidence of CHF and the decline in left ventricular ejection fraction (LVEF) were increased in patients receiving bevacizumab-awwb with anthracycline-based chemotherapy compared with patients receiving placebo with the same chemotherapy regimen.
    - The proportion of patients with a decline in LVEF from baseline of ≥20% or a decline from baseline of 10% to <50% was 10% in patients receiving bevacinumb-awwb plus chemotherapy compared with 5% in patients receiving chemotherapy alone.
    - Time to onset of left ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the bevacizumab-awwb arm compared with 82% in the placebo arm.
    - Discontinue bevacizumab-awwb in patients who develop CHF.

CONFERENCE HIGHLIGHTS

EARLY DOSE REDUCTIONS in a common adjuvant chemotherapy regimen were associated with inferior survival outcomes in a retrospective study of women with intermediate- to high-risk breast cancer (N = 1302) that evaluated chemotherapy total cumulative dose (TCD) and early versus late dose reductions.

The study used Alberta Cancer Registry data from women with diagnoses of stage I to stage III hormone receptor–positive/–negative, HER2-negative breast cancer who were treated with 5-fluorouracil/epirubicin/cyclophosphamide followed by docetaxel (FEC-D). Investigators concluded that sustaining TCD ≥85% is important for optimal clinical benefit.

Late dose reductions had “minimal” effect on disease-free survival (DFS) and overall survival (OS), the investigators said.

In their evaluation of TCD thresholds of ≥85% versus <85%, the investigators noted superior DFS at 5 years (86.9% vs 79.2%; P = .025) and superior OS at 5 years (88.8% vs 80.7%; P < .001) for those who received FEC-D at a TCD of ≥85%. A minority of the population (16%; n = 202) received FEC-D at a TCD <85%. The remaining 84% (n = 1100) received the adjuvant chemotherapy at ≥85%.

The differences were consistent in univariate and multivariate analyses. Specifically, a TCD of <85% compared with ≥85% was associated with a hazard ratio (HR) for progression of 1.45 (P = .040) and an HR for death of 1.50 (P = .043). Consequently, medical oncologists should strive to deliver full-dose FEC when prescribing the chemotherapy regimen, investigators said.

Because survival outcomes for the full-dose and LCD cohorts were equivalent, and those for ECD were inferior to both, investigators assessed the effect of a reduction in D using the ≥85% or <85% cutpoint for patients who had full-dose FEC and those who had any reduction in FEC. They sorted patients into 4 cohorts: FEC <100%/D ≥85% early cumulative dose (ECD1), FEC <100%/D ≥85% (ECD2), FEC = 100%/D ≥85% late cumulative dose (LCD1), and FEC = 100%/D ≥85% (LCD2).

DOSING COHORTS

<table>
<thead>
<tr>
<th>Dosing Cohort</th>
<th>DFSa</th>
<th>OSb</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECD1</td>
<td>78.9%</td>
<td>83.5%</td>
</tr>
<tr>
<td>ECD2</td>
<td>75.2%</td>
<td>75.2%</td>
</tr>
<tr>
<td>LCD1</td>
<td>85.5%</td>
<td>90.0%</td>
</tr>
<tr>
<td>LCD2</td>
<td>87.2%</td>
<td>87.9%</td>
</tr>
</tbody>
</table>

D indicates docetaxel, DFS, disease-free survival; ECD, early cumulative dose; FEC, fluorouracil, epirubicin, cyclophosphamide; LCD, late cumulative dose; OS, overall survival.

P = .002  *P < .001

ADVERSE EVENTS REPORT

Early Adjuvant Chemotherapy Dose Reductions Correlate With Poorer Survival in Breast Cancer

By RACHEL NAROZNIK, MA

EARLY DOSE REDUCTIONS in a common adjuvant chemotherapy regimen were associated with inferior survival outcomes in a retrospective study of women with intermediate- to high-risk breast cancer (N = 1302) that evaluated chemotherapy total cumulative dose (TCD) and early versus late dose reductions.

The study used Alberta Cancer Registry data from women with diagnoses of stage I to stage III hormone receptor–positive/–negative, HER2-negative breast cancer who were treated with 5-fluorouracil/epirubicin/cyclophosphamide followed by docetaxel (FEC-D). Investigators concluded that sustaining TCD ≥85% is important for optimal clinical benefit.

Late dose reductions had “minimal” effect on disease-free survival (DFS) and overall survival (OS), the investigators said.

In their evaluation of TCD thresholds of ≥85% versus <85%, the investigators noted superior DFS at 5 years (86.9% vs 79.2%; P = .025) and superior OS at 5 years (88.8% vs 80.7%; P < .001) for those who received FEC-D at a TCD of ≥85%. A minority of the population (16%; n = 202) received FEC-D at a TCD <85%. The remaining 84% (n = 1100) received the adjuvant chemotherapy at ≥85%.

The differences were consistent in univariate and multivariate analyses. Specifically, a TCD of <85% compared with ≥85% was associated with a hazard ratio (HR) for progression of 1.45 (P = .040) and an HR for death of 1.50 (P = .043). Consequently, medical oncologists should strive to deliver full-dose FEC when prescribing the chemotherapy regimen, investigators said.

Because survival outcomes for the full-dose and LCD cohorts were equivalent, and those for ECD were inferior to both, investigators assessed the effect of a reduction in D using the ≥85% or <85% cutpoint for patients who had full-dose FEC and those who had any reduction in FEC. They sorted patients into 4 cohorts: FEC <100%/D ≥85% early cumulative dose (ECD1), FEC <100%/D ≥85% (ECD2), FEC = 100%/D ≥85% late cumulative dose (LCD1), and FEC = 100%/D ≥85% (LCD2).

DOSING COHORTS

<table>
<thead>
<tr>
<th>Dosing Cohort</th>
<th>DFSa</th>
<th>OSb</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECD1</td>
<td>78.9%</td>
<td>83.5%</td>
</tr>
<tr>
<td>ECD2</td>
<td>75.2%</td>
<td>75.2%</td>
</tr>
<tr>
<td>LCD1</td>
<td>85.5%</td>
<td>90.0%</td>
</tr>
<tr>
<td>LCD2</td>
<td>87.2%</td>
<td>87.9%</td>
</tr>
</tbody>
</table>

D indicates docetaxel, DFS, disease-free survival; ECD, early cumulative dose; FEC, fluorouracil, epirubicin, cyclophosphamide; LCD, late cumulative dose; OS, overall survival.

P = .002  *P < .001

The worse survival trends in the ECD cohorts prompted the investigators to conclude that late reductions in chemotherapy did not have as much of an effect on DFS and OS compared with early reductions. They said the findings highlight the need to avoid chemotherapy dose reductions early in treatment.

Early dose reductions can be related to toxicities, such as febrile neutropenia, and may be associated with dose delays that result from the secondary use of granulocyte colony-stimulating factors, dose capping for high body surface area relating to obesity, and comorbidities, the authors said.

The retrospective nature of the study rendered accurate evaluation of the reasons for dose reduction difficult, the authors added, but they hypothesized that some of the early dose reductions among the study population were related to dose capping.

Patients eligible for evaluation were those who received a cancer diagnosis between 2007 and 2014 and received a minimum of 4 and maximum of 6 cycles of adjuvant FEC-D, with ≥1 cycle of D.

The patients who received a TCD ≥85% were more likely to be younger (median age of 54 versus 57 years; P < .001), be premenopausal (44.5% vs 28.2%; P < .001), and have fewer comorbidities (84.5% vs 72.8%) than those treated with the lower TCD.

REFERENCE

Indication
VITRAKVI® (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information

Neurotoxicity: Among the 176 patients who received VITRAKVI, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively. The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Please see additional Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information.
**THE FIRST-IN-CLASS TRK* INHIBITOR FOR TRK FUSION CANCER ACROSS SOLID TUMORS**

**Indication**
VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

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

**Important Safety Information (continued)**
**Neurotoxicity (continued):** Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dose when resumed.

**Hepatotoxicity:** Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated.

**Embryo-Fetal Toxicity:** VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

**Most Common Adverse Reactions (≥20%):** The most common adverse reactions (≥20%) were: increased ALT (45%), increased AST (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%).
Across solid tumors

VITRAKVI IS HIGHLY EFFECTIVE IN TRK FUSION CANCER

Powerful response across multiple tumor types (as assessed by a BIRC, N=55)

![Graph showing efficacy](image)

- **22% CR** (n=12)
- **53% PR** (n=29)
- **75% ORR** (95% CI: 61%, 85%) (n=41/55)

*Includes one pediatric patient with unresectable IFS who underwent resection following partial response and who remained disease-free at data cutoff.*

Median DOR not reached at time of data cutoff (N=41)

- **Range: 1.6+ to 33.2+ months**

Test for actionable alterations, including NTRK gene fusion. TEST. TRK. TREAT.

Select patients for treatment with VITRAKVI based on the presence of an NTRK gene fusion in tumor specimens. An FDA-approved test for NTRK gene fusion is not currently available.

**Study design:** 55 adult and pediatric patients with unresectable or metastatic solid tumors with an NTRK gene fusion were included for the pooled efficacy analysis across the multicenter, open-label, single-arm clinical studies: LOXO-TRK-14001, NAVIGATE, and SCOUT. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease.

**Major efficacy outcome measures:** ORR and DOR, as determined by a BIRC according to RECIST version 1.1.

**Important Safety Information (continued)**

**Drug Interactions:** Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John’s wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

**Lactation:** Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

**Please see Brief Summary of full Prescribing Information on the following page.**

Visit VITRAKVI.com
VITRAKVI® (larotrectinib) capsules, for oral use
VITRAKVI® (larotrectinib) oral solution

Initial U.S. Approval: 2018

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that:

• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,
• are metastatic or where surgical resection is likely to result in severe morbidity, and
• have no satisfactory alternative treatments or that have progressed following treatment.

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Neurotoxicity
Among the 176 patients who received VITRAKVI, neurologic adverse reactions of any grade occurred in 33% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively [see Adverse Reactions (6.1)].

The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysesthesia (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed [see Dosage and Administration (2.3)].

5.2 Hepatotoxicity
Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients [see Adverse Reactions (6.1)]. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed [see Dosage and Administration (2.3)].

5.3 Embryo-Fetal Toxicity
Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise women of the reproductive risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI [see Use in Specific Populations (8.1, 8.3)].

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

• Neurotoxicity [see Warnings and Precautions (5.1)]
• Hepatotoxicity [see Warnings and Precautions (5.2)]

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

Data in WARNINGS AND PRECAUTIONS and below reflects exposure to VITRAKVI in 176 patients, including 70 (40%) patients exposed for greater than 6 months and 35 (20%) patients exposed for greater than 1 year. VITRAKVI was studied in one adult dose-finding trial (LOXO-TRK-14001 (n = 70)), one pediatric dose-finding trial (SCOUT (n = 43)), and one single arm trial (NAVIGATE (n = 63)). All patients had an unresectable or metastatic solid tumor and no satisfactory alternative treatment options or disease progression following treatment.

Across these 176 patients, the median age was 51 years (range: 18 to 92 years); 53% were 18 years or younger; 34% were White, 11% were Hispanic/Latino, 8% were Black, and 3% were Asian. The most common tumors in order of decreasing frequency were soft tissue sarcoma (10%), salivary gland (11%), lung (10%), thyroid (9%), colon (8%), infantile fibrosarcoma (8%), primary central nervous system (CNS) (7%), and melanoma (5%). NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Most adults (80%) received VITRAKVI 100 mg orally twice daily and 68% of pediatrics (18 years or younger) received VITRAKVI 100 mg/m² twice daily up to a maximum dose of 100 mg twice daily. The dose ranged from 50 mg daily to 200 mg twice daily in adults and 9.6 mg/m² twice daily to 120 mg/m² twice daily in pediatrics [see Pediatric Use (4.4)].

The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, nausea, dizziness, vomiting, anemia, increased AST, cough, increased ALT, constipation, and diarrhea.

The most common serious adverse reactions (≥ 2%) were pyrexia, diarrhea, sepsis, abdominal pain, dehydration, cellulitis, and vomiting. Grade 3 or 4 adverse reactions occurred in 51% of patients; adverse reactions leading to dose interruption or reduction occurred in 37% of patients and 13% permanently discontinued VITRAKVI for adverse reactions.

The most common adverse reactions (1%-2%) that resulted in discontinuation of VITRAKVI were brain edema, intestinal perforation, pericardial effusion, pleural effusion, small intestinal obstruction, dehydration, fatigue, increased ALT, increased AST, enterocutaneous fistula, increased amylase, increased lipase, muscular weakness, abdominal pain, asthma, decreased appetite, dyspnea, hypotension, jaundice, syncope, vomiting, acute myeloid leukemia, and nausea.

The most common adverse reactions (≥ 3%) resulting in dose modification (interruption or reduction) were increased ALT (8%), increased AST (6%), and dizziness (3%). Most (82%) adverse reactions leading to dose modification occurred during the first three months of exposure.

Adverse reactions of VITRAKVI occurring in ≥ 10% of patients and laboratory abnormalities worsening from baseline in ≥ 5% of patients are summarized in Table 2 and Table 3, respectively.

### Table 2 Adverse Reactions Occurring in ≥ 10% of Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VITRAKVI N = 176</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td><strong>All Grades</strong></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>28</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>10</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>15</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>13</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
</tr>
</tbody>
</table>

*Hypertension:* Blood pressure increase ≥ 150 mm Hg systolic or ≥ 90 mm Hg diastolic.

### Table 3 Laboratory Abnormalities Occurring in ≥ 5% Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>VITRAKVI*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades</strong></td>
<td><strong>Grade 3-4</strong></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased AST</td>
<td>45</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>35</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>30</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>42</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23</td>
</tr>
</tbody>
</table>

*For each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 170 to 174 patients.

**NCI-CTCAE = v 4.03**
7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VITRAKVI

Strong CYP3A4 Inducers

Co-administration of VITRAKVI with a strong CYP3A4 inducer may increase
larotrectinib plasma concentrations, which may result in a higher incidence of adverse
reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of
VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit
juice. If co-administration of strong CYP3A4 inhibitors cannot be avoided, modify
VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

Strong CYP3A4 Inducers

Co-administration of VITRAKVI with a strong CYP3A4 inducer may decrease
larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI
[see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with
strong CYP3A4 inducers, including St. John's wort. If co-administration of strong
CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended
[see Dosage and Administration (2.5)].

7.2 Effects of VITRAKVI on Other Drugs

Sensitive CYP3A4 Substrates

Co-administration of VITRAKVI with sensitive CYP3A4 substrates may increase
their plasma concentrations, which may increase the incidence or severity of
adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of
VITRAKVI with sensitive CYP3A4 substrates. If co-administration of these
sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased
adverse reactions of these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on literature reports in human subjects with congenital mutations leading
to changes in TRK signaling, findings from animal studies, and its mechanism of
action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryofetal
harm when administered to a pregnant woman. There are no available data on
VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats
resulted in malformations at maternal exposures that were approximately 11- and 0.7-times,
respectively, those observed at the clinical dose of 100 mg twice daily (see Data).
Adverse reactions observed at the potential risk to a fetus in rats

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

Human Data

Published reports of individuals with congenital mutations leading to
changes in TRK signaling, findings from animal studies, and its mechanism of
action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryofetal
harm when administered to a pregnant woman. There are no available data on
VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats
resulted in malformations at maternal exposures that were approximately 11- and 0.7-times,
respectively, those observed at the clinical dose of 100 mg twice daily (see Data).
Adverse reactions observed at the potential risk to a fetus in rats

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

Larotrectinib crosses the placenta in animals. Larotrectinib did not result in
embryolethality at maternally toxic doses [up to 40 times the human exposure
based on area under the curve (AUC) at the clinical dose of 100 mg twice daily] in
embryo-fetal development studies in pregnant rats dosed during the period of
organogenesis; however, larotrectinib was associated with fetal anasarca in rats
from dams treated at twice-daily doses of 40 mg/kg [11 times the human exposure
(AUC) at the clinical dose of 100 mg twice daily]. In pregnant rabbits, larotrectinib
administration was associated with omphalocole at twice-daily doses of 15 mg/kg
(0.7 times the human exposure at the clinical dose of 100 mg twice daily).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating
VITRAKVI [see Use in Specific Populations (8.1)].

Contraception

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

Females

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

Males

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

Infertility

Females

Based on histopathological findings in the reproductive tracts of female rats in
a 1-month repeated-dose study, VITRAKVI may reduce fertility [see Nonclinical
Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of VITRAKVI in pediatric patients was established
based upon data from three multicenter, open-label, single-arm clinical trials in
adult or pediatric patients 28 days and older [see Adverse Reactions (6.1),
Clinical Studies (14)].

The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in
the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was
evaluated in 44 pediatric patients who received VITRAKVI. Of these 44 patients,
27% were 1 month to < 2 years (n = 12), 43% were 2 years to < 12 years (n = 19),
and 30% were 12 years to < 18 years (n = 13). 43% had metastatic disease
and 57% had locally advanced disease; and 91% had received prior treatment for
their cancer, including surgery, radiotherapy, or systemic therapy. The most common
adverse reactions were infantile fibrosarcoma (37%), soft tissue sarcoma (29%), primary
CNS tumors (20%), and thyroid cancer (9%). The median duration of exposure was
5.4 months (range: 9 days to 1.9 years).

Due to the small number of pediatric and adult patients, the single arm design of
clinical studies of VITRAKVI, and confounding factors such as differences in
susceptibility to infections between pediatric and adult patients, it is not possible to
determine whether differences in the incidence of adverse reactions to VITRAKVI
are related to patient age or other factors. Adverse reactions and laboratory
abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5%
increase in per-patient incidence) in pediatric patients compared to adult patients
were increased weight (11% vs. 2%) and neutropenia (20% vs. 2%). One of
the 44 pediatric patients discontinued VITRAKVI due to an adverse reaction (Grade 3
increased ALT).

8.5 Geriatric Use

Of 176 patients in the overall safety population who received VITRAKVI, 22% of
patients were ≥ 65 years of age and 5% of patients were ≥ 75 years of age. Clinical
studies of VITRAKVI did not include sufficient numbers of subjects aged 65 and
over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment
(CI-
Pugh B) to severe (Child-Pugh C) hepatic impairment [see Clinical
Pharmacology (12.3)].

8.7 Renal Impairment

No dose adjustment is recommended for patients with renal impairment of any
severity [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

Advises patients to notify their healthcare provider if they experience new or
worsening neurotoxicity. Advise patients not to drive or operate hazardous
machinery if they are experiencing neurologic adverse reactions [see Warnings
and Precautions (5.1)].

Advises patients that they will need to undergo laboratory tests to monitor liver
function [see Warnings and Precautions (5.2)].

Advises patients to notify their healthcare provider if they experience new or
worsening neurotoxicity. Advise patients not to drive or operate hazardous
machinery if they are experiencing neurologic adverse reactions [see Warnings
and Precautions (5.1)].

Advises patients that they will need to undergo laboratory tests to monitor liver
function [see Warnings and Precautions (5.2)].

Advises patients to notify their healthcare provider if they experience new or
worsening neurotoxicity. Advise patients not to drive or operate hazardous
machinery if they are experiencing neurologic adverse reactions [see Warnings
and Precautions (5.1)].

Advises patients to notify their healthcare provider if they experience new or
worsening neurotoxicity. Advise patients not to drive or operate hazardous
machinery if they are experiencing neurologic adverse reactions [see Warnings
and Precautions (5.1)].
BRCA Rules
Leave Patients Behind

by MEIR RINDE

SYNOPSIS

More than 20 years since the discovery of BRCA mutations, the debate over use of these as predictive markers continues. In breast, ovarian, tubal, and peritoneal cancers, testing for BRCA1/2 mutations has achieved mainstream acceptance, but clear direction is still lacking on which populations need to be tested and whether counseling on genetic testing should occur before or after. Time and evidence may be the sole factors that can resolve this issue.

KEY ISSUES

There is a need for more awareness of subpopulations at risk for BRCA1/2 mutation–driven cancers. More inclusive BRCA1/2 testing policies may better serve these patient populations.

UPDATED GUIDELINES from the United States Preventive Services Task Force (USPSTF) on BRCA1/2 genetic testing recommend risk assessment, counseling, and genetic testing for women who meet certain criteria but fall short of encompassing important groups of individuals who are at risk for developing BRCA1/2 mutation–driven disease, according to critics of the update.

For example, the USPSTF added ancestry associated with pathogenic BRCA1/2 gene variants as a criteria for assessment and genetic testing, and emphasized the use of trained health professionals for genetic counseling, including trained primary care providers. Yet critics say the guideline does not adequately consider some ethnic groups with high incidence of mutations, does not address access to and costs of testing, and rules out broader population-based testing based on an excessive concern over the potential harms of testing, among other issues (FIGURE 1-9).

The new guideline was published in August to update the USPSTF’s 2013 recommendations on BRCA assessment. It recommends that primary care clinicians use a familial risk assessment tool to assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancers or who have an ancestry associated with BRCA1/2 gene mutations. The panel said women with a positive result on the tool should receive genetic counseling and, if indicated, testing.

“It is a conservative move toward appropriate guideline-based testing,” said Allison Kurian, MD, MSc, director of the Stanford Women’s Clinical Cancer Genetics Program at Stanford University, in Palo Alto, California.

Many patients who were treated for breast and ovarian cancer decades ago “had fallen through the cracks” and never underwent genetic tests that are now standard, said Susan M. Domchek, MD, executive director of the Basser Center for BRCA at the University of Pennsylvania in Philadelphia. Testing for pathogenic mutations in the BRCA DNA-repair genes remains underused even among patients who have had those cancers more recently.

PATIENTS WITH A HISTORY OF CANCER

“We’re not doing as well as we can for the patients who are at the highest risk of having BRCA1 and 2 mutations,” Domchek said. “It requires all of us to take a minute and say, ‘This is my patient. She’s here for her hypertension, but she had ovarian cancer 15 years ago and I don’t think she’s gotten genetic testing.’ It’s really kind of putting this in the forefront for everyone.”

The USPSTF recommendations are largely consistent with National Comprehensive Cancer Network guideline, which recommends that breast cancer survivors be considered for BRCA1/2 testing if they meet at least 1 additional criterion, including diagnosis at age 45 or younger, diagnosis between 45 and 50 with family history of breast or prostate cancer or an unknown family history, diagnosis of additional breast cancers, or Ashkenazi Jewish heritage.
The NCCN guideline on genetic/familial high-risk assessment for breast and ovarian cancer also says patients who have had ovarian, pancreatic, metastatic prostate, or male breast cancer should be tested, as should men who have had high-grade prostate cancer if they meet 1 of several additional criteria. The NCCN also recommends that people from families with a known BRCA1/2 pathogenic or likely pathogenic variant be considered for testing. Unlike the NCCN, however, the USPSTF does not offer any recommendation regarding BRCA assessment in male patients, because evidence on the benefits and harms of genetic testing in men was not reviewed as part of the update. The USPSTF also declined to recommend population-based testing for BRCA1/2 mutations, saying that more research is needed.

J. Leonard Lichtenfeld, MD, MACP, deputy chief medical officer for the American Cancer Society, also called the USPSTF recommendation “conservative,” noting its lack of attention to male patients and population-based testing, and its recommendation of genetic counseling before testing. But, he said, it usefully highlights the importance of considering patients’ family histories.

“We, as health professionals, have done a pretty poor job of not only [asking about] family history, but [also] paying attention to family histories. It’s one thing to have someone take a family history and put it in a medical record. It’s quite another for someone to actually take a look at that family history and raise the question of whether someone should be tested,” Lichtenfeld said.

In the general population, BRCA1/2 mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancers, according to studies cited by the USPSTF. BRCA mutations raise breast cancer risk 45% to 65% by age 70. Risk of ovarian, fallopian tube, or peritoneal cancers increases to 39% for BRCA1 mutations and 17% for BRCA2 mutations.

Potentially harmful BRCA1/2 mutations occur in 0.2% to 0.3% of all women, while estimated prevalence is 6% in women with cancer onset before age 40 and 2.1% among women of Ashkenazi Jewish descent.

NOT ENOUGH TESTING

Kurian said increasing awareness of assessment and testing is an urgent matter because current testing rates are so low (FIGURE 2). A study she coauthored found that less than a quarter of patients with breast cancer (24.1%) and a third of those with ovarian cancer (30.9%) had genetic test results.4 Also, when tested for all genes that current guidelines designate as associated with their cancer type, 7.8% of patients with breast cancer and 14.5% of those with ovarian cancer had pathogenic variants.

“Patients with ovarian cancer absolutely should get genetic testing. There’s just no question; that’s been known and accepted in lots of guidelines for 10 years or more. We found, egregiously, that these patients are grossly undertested. Only 30% get tested when 100% should,” Kurian said.

The study included all women 20 years or older with diagnosed breast or ovarian cancer in California and Georgia between 2013 and 2014 and reported to the Surveillance, Epidemiology, and End Results registries. There were 77,085 patients with breast cancer and 6001 with ovarian cancer.

The study also found racial and economic disparities. Among those with ovarian cancer, testing rates were lower in black patients (21.6%, 95% CI, 18.1%-25.4%) than in whites (33.8%; 95% CI, 32.3%-35.3%), and in uninsured patients (20.8%; 95% CI, 15.5%-26.9%) versus insured patients (35.3%; 95% CI, 33.8%-36.9%). Prevalent pathogenic variants in patients with breast cancer were BRCA1 (3.2%), BRCA2 (3.1%), CHEK2 (1.6%), PALB2 (1.0%), ATM (0.7%), and NBR (0.4%); in patients with ovarian cancer, they were BRCA1 (8.7%), BRCA2 (5.8%), CHEK2 (1.4%), BRIPI (0.9%), MSH2 (0.8%), and ATM (0.6%).

Positive BRCA1/2 status can inform preventive care and shape treatment decisions for patients with breast, ovarian, prostate, and pancreatic cancers and with melanoma, according to the Basser Center. For women with BRCA mutations who have not had cancer, periodic breast exams, breast magnetic resonance imaging (MRI), and mammograms are recommended; male carriers should have breast exams, prostate exams, and prostate-specific antigen blood tests, also according to Basser. Both men and women should be examined annually by a dermatologist and may consider screening for pancreatic cancer.

**FIGURE 1. UPDATED USPSTF GUIDELINE LEAVES OUT KEY POPULATIONS**

<table>
<thead>
<tr>
<th>USPSTF guideline specifically addresses:</th>
<th>USPSTF guideline generally addresses:</th>
<th>Select high-risk groups not specifically mentioned in USPSTF guideline:</th>
</tr>
</thead>
</table>
| Women with family histories of breast, ovarian, tubal, or peritoneal cancer:  
  • BRCA1/2 mutations occur in 5%-10% of breast cancer cases and 15% of ovarian cancer cases.  
  • BRCA1/2 mutations increase breast cancer risk by 45%-65% by age 70 years.  
  • BRCA1 mutations increase risk of ovarian, fallopian tube, or peritoneal cancer by 39%  
| Ethnicities and ancestries associated with BRCA1/2 mutations:  
  • BRCA1/2 mutations occur in 6% of women with cancer onset before age 40 and 2.1% of women of Ashkenazi Jewish descent.  
  • BRCA2 mutations’ prevalence was 19.8% in a meta-analysis of studies with recruitment based on family history of breast or ovarian cancer.  
| • African Americans: BRCA1/2 mutations have been identified in 12%-18% with breast cancer  
  • Hispanic high-risk patients in the Southwest region of the United States: BRCA1/2 mutation rates were as high as 25% in patients of Mexican descent with a family history of breast or ovarian cancer  
  • Indian descent: Mutation rates were as high as 25% in patients with breast or ovarian cancer.  

USPSTF indicates United States Preventive Services Task Force.
BRCA TESTING

Women with BRCA mutations may also consider using chemopreventive drugs such as tamoxifen, which reduces the risk of developing hormone receptor–positive breast cancer in high-risk patients; raloxifene; or an aromatase inhibitor. Other options are prophylactic mastectomy, which reduces risk of breast cancer in high-risk women by about 90%, and removal of the ovaries and fallopian tubes, which reduces breast cancer risk by up to 50% and reduces ovarian cancer risk by 80%.7

Among women with diagnosed breast cancer, BRCA1 carriers are more likely to develop triple-negative cancers that require chemotherapy. They are at increased risk of developing second breast cancers and may want to consider mastectomy. BRCA1/2 mutation carriers may also benefit from use of PARP inhibitors. Olaparib (Lynparza) and talazoparib (Talzenna) are approved for treatment of certain metastatic breast cancers, and olaparib, rucaparib (Rubraca), and niraparib (Zejula) are approved for ovarian cancer. PARP inhibitors are also being studied for treatment of prostate, colorectal, pancreatic, skin, and non–small cell lung cancers.

CALLS FOR A BROADER GUIDELINE

In an editorial accompanying the USPSTF statement, Domchek and co-author Mark E. Robson, MD, chief of the Breast Medicine Service at Memorial Sloan Kettering Cancer Center in New York, New York, note that the new recommendation does not mention the relevance of BRCA1/2 status to decision making for patients with newly diagnosed early stage breast cancer and for determining treatment of advanced cancers. They called for consideration of further expansion of the recommendation.

“In ovarian cancer now, if you have a BRCA1 or 2 mutation, your ovarian cancer will be treated differently from the beginning. It all of a sudden becomes critically important that that information is known,” Domchek said.

Knowledge of BRCA status also allows prospective parents to avoid passing mutations on to their children, she said. They can choose to do in vitro fertilization and preimplantation genetic diagnosis to screen out embryos that carry germline BRCA1/2 mutations.

Domchek and Robson note that although the USPSTF recommendation adds ancestry associated with BRCA1/2 mutations as a risk factor, it does not specifically endorse testing for unaffected Ashkenazi Jewish women with no family history of relevant cancers. Results of studies of genetic testing in Ashkenazi Jews have shown that up to 50% of those found to have a pathogenic variant had no or minimal family history (ie, they have a small family with few women who reached high-risk age). However, the USPSTF statement “may be interpreted as a step toward supporting unselected testing” in Ashkenazi Jews, Domchek and Robson write.

African Americans and Hispanic women also have a well-documented high incidence of BRCA1/2 mutations, and these groups are not adequately represented in the USPSTF recommendations for risk assessment or genetic testing, according to critics.10

The USPSTF recommends against routine risk assessment or genetic testing for women who do not meet its criteria, citing potential harms from assessment, testing, and use of risk-reducing interventions that outweigh the benefits. Pat W. Whitworth, MD, a breast cancer surgeon at Saint Thomas Health in Nashville, Tennessee, said that position leaves the task force’s recommendation “way behind what needs to be happening.” He argued that the potential harms are minimal and noted that studies of unselected populations have found that about half of BRCA1/2 carriers detected do not meet published guidelines for clinical testing.11

“It’s always nice to see a step forward from the organizations that write guidelines, but this field is moving forward too quickly for guidelines to keep up. The guidelines for testing people are really functioning as a barrier,” said Whitworth, who helped craft a more expansive testing recommendation for the American Society of Breast Surgeons (ASBrS). In March, the ASBrS recommended that genetic testing for BRCA1/2 and other actionable alterations be made available to all patients with new diagnoses of breast cancer.12

Whitworth said BRCA1/2 testing via multigene panel testing (MGPT) should be done for all patients with breast cancer, followed by cascade testing of family members when appropriate, rather than testing only those who meet existing guidelines. He said that recommendation is supported by a clinical registry study he co-authored that used an 80-gene panel to test 959 patients with breast cancer, half of whom met NCCN screening guidelines. The investigators found pathogenic or likely pathogenic mutations in 9.39% of those who met the guidelines and 7.9% of those who did not, a difference that was not statistically significant ($P = .4241$).13

However, in another article, Domchek...
and Robson note that Whitworth and his colleagues found pathogenic variants of BRCA1/2 specifically in only 3 of 480 patients who did not meet testing guidelines. The positive rate of the in-guideline group was 4 times higher (2.51% vs 0.63%; P = 0.0201).

**GENETICS TRAINING IS LAGGING**

Large-panel gene testing has dropped sharply in cost and is becoming common in oncology—although it remains controversial. Domchek and Robson acknowledge that panel testing has largely replaced BRCA1/2-only tests, but they argue in their editorital that “the clinical utility of the indiscriminate use of MGPT has not been established, and genetics education of primary care clinicians has not kept pace with either the influx of new information or the changes in the genetic testing marketplace.”

Domchek cited several concerns about the widespread use of panel testing to detect BRCA mutations. They include the low incidence of BRCA1 mutations in unselected populations, the low or uncertain utility of knowing other types of mutations, the cost of testing, and the potential harms from unnecessary prophylactic surgery and of overuse of magnetic resonance imaging in follow-up screening.

Whitworth responded by pointing to a new modeling study of unselected BRCA1/BRCA2/PALB2 testing at breast cancer diagnosis published in *JAMA Oncology*. Using data from 11,836 women in the United Kingdom and United States, investigators concluded unselected testing was “extremely cost-effective” compared with testing based on clinical criteria or family history. The incremental cost-effectiveness ratio to test all US patients with breast cancer was $65,661 per quality-adjusted life year (QALY) from the payer perspective and $61,618/QALY from the societal perspective, well below standard thresholds. One year’s unselected panel genetic testing could prevent 2101 cases of breast or ovarian cancer and 633 deaths in the United Kingdom, and 9733 cases and 2406 deaths in the United Kingdom, and 2101 cases of breast or ovarian cancer and 633 deaths in the United Kingdom, and 9733 cases and 2406 deaths in the United Kingdom, and 2101 cases of breast or ovarian cancer.

**REFERENCES**


In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:

29% reduction in risk of PFS event*
(HR: 0.71; 95% CI: 0.54, 0.93; P = 0.011); median PFS 48.2 vs 20.8 months for A+CHP and CHOP, respectively; primary endpoint
*PFS was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease.

Indication
ADCETRIS® (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

Important Safety Information

BOXED WARNING
PROGRESSIVE MULTIFOCALE LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Contraindication
ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

WARNINGS AND PRECAUTIONS
- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
**reduction in risk of death**

(HR = 0.66; 95% CI: 0.46, 0.95; P = 0.024); key secondary endpoint

†Median overall survival follow-up of 42.1 months with A+CHP and CHOP; median overall survival not reached in either treatment arm.

**ECHELON-2 trial design:** A multicenter, phase 3, randomized, double-blind, double-dummy, actively controlled trial in 452 patients with sALCL and other CD30-expressing PTCL. Patients were randomized 1:1 to A+CHP (n = 226) or CHOP (n = 226), and received treatment every 3 weeks for 6 to 8 cycles at investigator’s discretion. Primary endpoint was PFS per IRF, defined as progression, death from any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease. Overall survival was a key secondary endpoint.

**Most common adverse reactions (≥20%) in combination with CHP**

Anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

A+CHP = ADCETRIS + cyclophosphamide, doxorubicin, prednisone; sALCL = anaplastic large cell lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHP = cyclophosphamide, doxorubicin, prednisone; CI = confidence interval; HR = hazard ratio; IRF = independent review facility; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages. Full Prescribing Information available at adcetrispro.com
Important Safety Information, cont’d

- Anaphylaxis and infusion reactions: Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS® (brentuximab vedotin). Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

- Hematologic toxicities: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (>1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma or previously untreated PTCL.

  Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

- Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.

- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor and high tumor burden.

- Increased toxicity in the presence of severe renal impairment: The frequency of >Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.

- Increased toxicity in the presence of moderate or severe hepatic impairment: The frequency of >Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.

- Hepatotoxicity: Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- PML: Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

- Pulmonary toxicity: Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

- Serious dermatologic reactions: Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- Gastrointestinal (GI) complications: Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

- Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Most Common (≥20% in any study)
Adverse Reactions

Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

Drug Interactions

Concomitant use of strong CYP3A4 inhibitors or inducers has the potential to affect the exposure to monomethyl auristatin E (MMAE).

Use in Specific Populations

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use. Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages and full Prescribing information at adcetrispro.com


NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
JC virus infection resulting in PML and death can occur in patients receiving ADCEITRS.

1 INDICATIONS AND USAGE
ADCEITRS is a CD10-directed antibody-drug conjugate indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or cutaneous expressing peripheral T-cell lymphomas (PTCL), including angiomatoid CD10-expressing peripheral T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
For dosing instructions concerning combination agents administered with ADCEITRS, see the manufacturer’s prescribing information.

Monitor complete blood counts prior to each dose of ADCEITRS. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCEITRS doses.

5.4 Serious Infections and Opportunistic Infections
Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCEITRS. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome
Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment
The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCEITRS in patients with severe renal impairment (Ccr <30 mL/min).

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment
The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCEITRS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

5.8 Hepatotoxicity
Focal and serious cases of hepatotoxicity have occurred in patients receiving ADCEITRS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Gains have occurred after the first dose of ADCEITRS or after ADCEITRS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCEITRS.

5.9 Progressive Multifocal Leukoencephalopathy
Focal cases of JC virus infection resulting in PML have been reported in ADCEITRS-treated patients. First onset of symptoms occurred at various times from initiation of ADCEITRS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCEITRS therapy, other potential contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCEITRS dosing for any suspected case of PML and discontinue ADCEITRS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity
Focal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS) have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCEITRS dosing during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions
Focal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCEITRS. If SJS or TEN occurs, discontinue ADCEITRS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications
Focal and serious events of acute pancreatitis have been reported. Other focal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, ADCEITRS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCEITRS in pregnant women. Animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicity, including significantly decreased embryo viability and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks. Advise females of reproductive potential to avoid pregnancy during ADCEITRS treatment and for at least 8 months after the final dose of ADCEITRS. Advise a pregnant woman of the potential risk to the fetus.

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The most common adverse reactions (≥20%) in combination with CHOP were anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

Previously Untreated SACL or Other CD30-Expressing PTCL (Study 6, ECHELON-2)

ADCCERIS in combination with CHOP was evaluated in patients with previously untreated, CD30-expressing PTCL in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. Patients were randomized to receive ADCCERIS + CHOP or CHOP for 8 to 21-day cycles. ADCCERIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHOP. The trial required hepatic transaminases ≤3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy. A total of 469 patients were treated (223 with ADCCERIS + CHOP, 226 with CHOP), with 8 cycles planned in 87% of patients. ADCCERIS + CHOP arm, 70% of patients received 8 cycles, and 18% received 8 cycles. Primary prophylaxis with G-CSF was administered to 84% of ADCCERIS + CHOP-treated patients and 27% of CHOP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the AV-Chop arm and in 4% of patients in the CHOP arms, most often from infection. Serious adverse reactions were reported in 38% of patients with CHOP-treated patients and 35% of CD30-treated patients. Serious adverse reactions occurring in >2% of patients with CHOP-treated patients included febrile neutropenia (14%), pneumonia (6%), pyrexia (5%), and sepsis (3%).

The most common adverse reactions observed >2% more in recipients of ADCCERIS + CHOP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥10%) adverse reactions observed >2% more in recipients of ADCCERIS + CHOP were febrile neutropenia, diarrhea, abdominal pain, decreased appetite, dyspnea, edema, cough, dysgeusia, pyrexia, decreased weight, and myelophagia. In recipients of ADCCERIS + CHOP, adverse reactions led to dose delays of ADCCERIS in ~14% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCCERIS with or without the other components in 7% (most often from peripheral neuropathy and infection).

Table 7: Adverse Reactions Reported in ≥10% of ADCCERIS + CHOP-Treated Patients with Previously Untreated CD30-Expressing PTCL (Study 6: ECHELON-2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCCERIS + CHOP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Lymphopenia*</td>
<td>61</td>
<td>18</td>
</tr>
<tr>
<td>Fever or neutropenia</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Mucositis</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 7: Adverse Reactions, cont'd

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCCERIS + CHOP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>12</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

*Derived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and end of treatment.

The table includes a combination of grouped and ungrouped terms. CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone. CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone. Events were graded using the NCICTCAE Version 4.03.

Additional Important Adverse Reactions

Infection Reactions

No infection-related reactions were reported in 10 patients (4%) in the ADCCERIS + CHOP-treated arm. 11% patients with events that were Grade 3 or higher events, and 8% (4%) patients with events that were less than Grade 3.

Pulmonary Toxicity

No patients with cHL that studied ADCCERIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial inflammation and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCCERIS with bleomycin is contraindicated.

In a study of ADCCERIS in combination with CHOP (Study 6, ECHELON-2), non-infectious pulmonary toxicity events were reported in 7% of the patients (2%) in the ADCCERIS + CHOP arm, all 9 events were pneumonitis.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCCERIS. 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: Febrile neutropenia.

Gastrointestinal disorders: Acute pancreatitis and gastrointestinal complications (including fatal outcomes).

Hepatobiliary disorders: Hepatotoxicity.

Infections: Pneumocystis carinii pneumonia and opportunistic infections.

Metabolism and nutrition disorders: Hypoglycemia.

Respiratory, thoracic and mediastinal disorders: Noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes).

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the test. 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 to ADCCERIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patients were either transiently or persistently positive for anti-brentuximab vedotin antibodies; 60% of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on ADCETRIS
CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MVAIE, which may increase the risk of adverse reactions. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every 4 weeks caused embryotoxic fetus-to-maternal body mass index (BMI) ratios, and included increased early resorption (<90%), post-implantation loss (10%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and multicystic kidneys). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation
Risk Summary
There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from ADCETRIS, including cryoparasias, erythrocytopenia, or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

Contraception
Females
Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

Males
ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential may also be exposed to effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility
Males
Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

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

8.5 Geriatric Use
In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD19-expressing PTCL, 91% of ADCETRIS + CHP-treated patients were age 65 or older. Among older patients, 74% had adverse reactions ≥Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 82% had adverse reactions ≥Grade 3 and 9% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 23% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment
Avoid the use of ADCETRIS in patients with severe renal impairment (CrCl <30 mL/min). No dosage adjustment is required for mild (CrCl ≥30–50 mL/min) or moderate (CrCl 10–30 mL/min) renal impairment.

8.7 Hepatic Impairment
Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment.

10 OVERdosage
There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

17 PATIENT COUNSELING INFORMATION
Peripheral Neuropathy: Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their healthcare provider any numbness or tingling of the hands or feet or any muscle weakness.

Fever/Neutropenia: Advise patients to contact their healthcare provider if a fever of 100°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

Infusion Reactions: Advise patients to contact their healthcare provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion.

Hepatotoxicity: Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Progressive Multifocal Leukoencephalopathy: Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms:
- Changes in mood or usual behavior
- Confusion, thinking problems, loss of memory
- Changes in vision, speech, or walking
- Decreased strength or weakness on one side of the body

Pulmonary Toxicity: Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath.

Acute Pancreatitis: Advise patients to contact their healthcare provider if they develop severe abdominal pain.

Gastrointestinal Complications: Advise patients to contact their healthcare provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea.

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

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

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcetris.com
Practice-changing findings from several phase III studies were featured at the annual meeting of the European Society for Medical Oncology (ESMO Congress 2019), which was held September 27 through October 1 in Barcelona, Spain. New data for PARP inhibitor therapy in recurrent ovarian cancer and castration-resistant prostate cancer are among the highlights. In breast cancer, results for trials of CDK4/6 inhibitors add to the growing body of evidence on the clinical utility of these agents. For more exclusive articles and videos, onclive.com/link/6578.

### Ovarian Cancer

**Niraparib Improves PFS as Frontline Maintenance in Ovarian Cancer**

by **Silas Inman**

**FRONTLINE MAINTENANCE THERAPY** with the PARP inhibitor niraparib (Zejula) improved median progression-free survival (PFS) by 5.6 months compared with placebo for patients with newly diagnosed advanced ovarian cancer who responded to platinum-based chemotherapy, according to findings from the phase III PRIMA study presented at the ESMO Congress 2019 and simultaneously published in the *New England Journal of Medicine.*

In the overall population of the PRIMA study, the median PFS in the niraparib arm was 13.8 months compared with 8.2 months in the placebo group, representing a 38% reduction in the risk of progression or death (HR, 0.62; 95% CI, 0.50–0.76; *P* < .001) with the addition of the PARP inhibitor (TABLE). In patients with tumors that tested positive for homologous recombination deficiency (HRD), the median PFS was 21.9 months with niraparib compared with 10.4 months for placebo (HR, 0.43; 95% CI, 0.50–0.76; *P* < .001).

“Niraparib therapy in patients with advanced ovarian cancer provided a clinically significant improvement in PFS after response to first-line platinum-based chemotherapy in all patients,” said study author Antonio Gonzalez-Martin, MD, from the Clinica Universidad de Navarra in Spain. “Niraparib is the first PARP inhibitor to demonstrate benefit in patients across biomarker subgroups after platinum-based chemotherapy in [the frontline setting], consistent with prior clinical studies of niraparib in recurrent ovarian cancer.”

The study randomized 733 patients in a 2:1 ratio to receive niraparib (n = 487) or placebo (n = 246). Patients were randomized within 12 weeks of finishing the last cycle of chemotherapy. At the initiation of the study, niraparib was given at a fixed dose of 300 mg, which was adjusted to include a lower dose of 200 mg for those weighing less than 77 kg and for those with platelet counts below 150 K/μL. The median relative dose intensity in the study was 63%. Gonzalez-Martin noted that future presentations will focus on the potential impact of this dose change.

Patient characteristics were similar across groups. The ECOG performance status was 1 for approximately 70% of patients, two-thirds had a FIGO stage of III, and a third had stage IV disease. The primary tumor locations were the ovary, fallopian tube, and peritoneum. Most patients had serous histology (approximately 95%).
Niraparib and 5.4 months for placebo (HR, 0.68; 95% CI, 0.49-0.94). Interim OS data for HRD-negative patients showed 81% and 59% 24-month OS rates, respectively (HR, 0.51; 95% CI, 0.27-0.97).

More patients experienced treatment-related adverse events (TRAEs) of any grade in the niraparib arm compared with placebo (96.3% vs 68.9%). Grade ≥3 TRAEs were experienced by 65.3% of patients in the niraparib arm compared with 6.6% of those in the placebo group. The most common AEs of grade ≥3 severity, respectively, were anemia (31.0% vs 1.6%), thrombocytopenia (28.7% vs 0.4%), platelet count decrease (13.0% vs 0%), and neutropenia (12.8% vs 1.2%).

Overall, 70.9% of patients required a dose reduction in the niraparib arm, and 12% of patients discontinued therapy due to AEs. The main AEs relating to discontinuation were myelosuppressive in nature, with 4.3% from thrombocytopenia.

Niraparib monotherapy is approved as a maintenance therapy in the recurrent ovarian cancer setting. This approval was granted in March 2017. In October, the FDA approved niraparib as a treatment for patients with BRCA- or HRD-positive ovarian cancer who have received 3 or more prior chemotherapy regimens and progressed more than 6 months after their last platinum-based chemotherapy.

### REFERENCES


Trametinib Demonstrates Efficacy in Recurrent, Low-Grade Ovarian Cancer

by ONCLIVE® STAFF

TREATMENT WITH THE MEK inhibitor trametinib (Mekinist) significantly improved progression-free survival (PFS) and led to a strong trend toward improved overall survival (OS) in recurrent low-grade serous ovarian cancer, the results of a randomized trial showed.

Median PFS improved from 7.2 months with current standard-of-care (SOC) options to 13.0 months with trametinib. OS also increased by 8 months, but just missed achieving statistical significance ($P = .054$).

More than 4 times as many patients achieved objective responses with the MEK inhibitor, and these responses last more than twice as long, as reported at the 2019 ESMO Congress.

“Our findings suggest that trametinib represents a new standard-of-care treatment option for women with recurrent low-grade serous carcinoma,” said David Gershenson, MD, of The University of Texas MD Anderson Cancer Center.

The significant PFS benefit and borderline survival improvement occurred despite 68% of patients in the SOC arm crossing over to trametinib at disease progression, said Jonathan Ledermann, MD, of University College London. Patients who crossed over to the MEK inhibitor also benefited, he added, as indicated by a median PFS of 10.8 months.

“Recurrent low-grade serous ovarian cancer responds very poorly to chemotherapy,” said Ledermann. “It has a long natural history, so evaluation of disease stabilization with interventions can be difficult.”

As if anticipating whether the results reflected a class effect of MEK inhibitors, Ledermann noted that a randomized trial of binimetinib (Mektovi) in recurrent serous ovarian cancer did not demonstrate superiority versus SOC, except in the subgroup of patients with KRAS mutations.

Low-grade serous ovarian or peritoneal cancer accounts for 5% to 10% of all serous ovarian cancers and may arise de novo or following a serous borderline tumor, Gershenson noted.

The condition is characterized by alterations in the MAP kinase pathway, relative chemoresistance, and prolonged OS compared with high-grade serous ovarian cancer.

A single-arm open-label trial of the investigational MEK inhibitor selumetinib showed preliminary evidence of activity in low-grade serous ovarian cancer, providing a rationale for additional clinical investigation of MEK inhibition in the disease.

Gershenson reported findings from a randomized phase II/III trial involving 260 patients with recurrent low-grade serous ovarian or peritoneal carcinoma. Patients were randomized to trametinib or to investigator’s choice of 5 SOC therapies: letrozole, tamoxifen, pegylated liposomal doxorubicin, paclitaxel, or topotecan. Eligible patients could have received any number of prior regimens, including at least 1 prior platinum regimen, but not all 5 SOC regimens in the trial’s control arm.

The primary end point was PFS, and secondary endpoints included toxicity, quality of life, objective response, and OS. Baseline characteristics were evenly distributed between the 2 groups, including a median age of 56, primary site in the ovary in 91% of patients, US residence for 79%, and performance status of 0 in 71.5%.

Additionally, 48% of patients had received at least 3 prior systemic regimens.

At data analysis, more than half of the patients (62.3%), but substantially fewer in the trametinib arm (42.3%) had discontinued treatment because of disease progression.

The primary analysis showed that patients treated with trametinib had a 52% reduction in the hazard for disease progression or death (HR, 0.48; 95% CI, 0.36-0.64; $P < .0001$). Trametinib led to objective responses in 26.2% of patients versus 6.2% in the control arm (OR, 5.4; $P < .0001$). The median duration of response was 13.6 months with the MEK inhibitor and 5.9 months with SOC.

The survival analysis yielded a median OS of 37.0 months for the trametinib arm and 29.2 months for the control group, representing a 25% reduction in the survival hazard (HR, 0.75; 95% CI, 0.51-1.11; $P = .054$).

With regard to treatment-emergent adverse events (AEs) of all grades, trametinib resulted in more cases of rash (92.1% vs 48.5%), fatigue (72.5% vs 57.8), diarrhea (72.4% vs 33.6%), nausea (60.6% vs 50.8%), anemia (51.9% vs 43.0%), vomiting (45.7% vs 34.4%), and hypertension (38.6% vs 21.2%). The most common grade ≥3 AEs in the trametinib arm were rash (15.0%), anemia (12.6%), hypertension (11.8%), and diarrhea (10.2%).

Among AEs of special interest for trametinib, decreased left ventricular ejection fraction (LVEF) was the most frequent (7.9%), followed by pneumonitis (2.4%), retinal vascular disorder, LVEF systolic dysfunction, UFe prolongation (all <2 events each), and retinal tear (0.8%).

As Ledermann noted, almost 70% of patients randomized to SOC crossed over to trametinib. Those 88 patients had a median PFS of 10.8 months, a 15% response rate, and a median response duration of 15.9 months.

REFERENCE

EXPLORE TIL IMMUNOTHERAPY

TIL MANUFACTURING AT IOVANCE STARTS WITH ISOLATING TUMOR-INFLTRATING LYMPHOCYTES (TIL)
from a surgically resected piece of a patient’s tumor. The isolated TIL, which may recognize multiple patient-specific antigens expressed by the tumor, are expanded to billions of cells. Prior to infusion of TIL, the patients are treated with non-myeloablative lymphodepletion preconditioning to remove the suppressive tumor micro-environment. Once the TIL are infused, the patients receive up to 6 doses of IL-2 to support expansion and anti-tumor activity of the TIL.

22 DAY PROCESS, ONE-TIME THERAPY

YOU OR SOMEONE YOU KNOW MAY QUALIFY FOR ONE OF OUR TIL THERAPY CLINICAL STUDIES IF INITIAL CRITERIA ARE MET:

- Diagnosis of:
  • Unresectable or metastatic melanoma, stage IIIC or IV
  • Locally advanced or metastatic NSCLC, stage III or IV
  • HPV + or - recurrent and/or metastatic HNSCC
  • Recurrent, metastatic or persistent cervical cancer
- At least one resectable tumor for TIL generation
- 18 years old or older
- ECOG PS 0-1

If these key eligibility criteria are met, you may be eligible to participate in our clinical study program. There are additional eligibility criteria that must be met and can only be assessed by a study physician.

TO LEARN MORE ABOUT THE TRIALS
Call 1-866-565-4410, and press option 3, email clinical.inquiries@iovance.com or, go to www.iovance.com/clinical/our-clinical-program

VISIT CLINICALTRIALS.GOV
Metastatic Melanoma: NCT02360579
Cervical Cancer: NCT03108495
Head and Neck Cancer: NCT03083873
Multiple Solid Tumors: NCT03645928
(Melanoma, HNSCC, NSCLC)

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and efficacy of this therapy has not been determined.
Frontline Veliparib Regimen Shows Intriguing PFS Findings

by SILAS INMAN

THE FRONTLINE COMBINATION of veliparib/carboplatin/paclitaxel followed by maintenance veliparib monotherapy led to a 32% reduction in the risk of progression or death compared with placebo plus chemotherapy with placebo maintenance for patients with high-grade serous ovarian cancer, according to results of the phase III VELIA study presented at the 2019 ESMO Congress and simultaneously published in the New England Journal of Medicine (NEJM).1,2

The study recruited patients with and without BRCA mutations (FIGURE).1 Across all subgroups, the median progression-free survival (PFS) for the induction plus maintenance phases in the veliparib arm was 23.5 months versus 17.3 months in the placebo arm (HR, 0.68; 95% CI, 0.56-0.83; P < .001).

The benefit was more pronounced for those with BRCA mutations. In this group, the median PFS was 34.7 months compared with 22.0 months for veliparib and placebo, respectively (HR, 0.44; 95% CI, 0.28-0.68; P < .001).

Another arm explored frontline veliparib plus chemotherapy followed by placebo maintenance; however, a benefit for veliparib was not demonstrated in this arm of the trial compared with chemotherapy plus placebo with placebo maintenance. Findings for this group were published in NEJM but not presented in full at the ESMO Congress.

“Veliparib added to chemotherapy and continued as maintenance significantly extended PFS in all patient cohorts with newly diagnosed high-grade serous ovarian carcinoma, regardless of biomarker, choice of surgery, or paclitaxel regimen,” said lead author Robert L. Coleman, MD, from The University of Texas MD Anderson Cancer Center (TABLE).

“Veliparib in combination with chemotherapy should be considered a new treatment option for women with newly diagnosed, advanced-stage serous ovarian cancer.”

The VELIA study randomized patients evenly between 3 arms: The first arm (control) consisted of carboplatin and paclitaxel with placebo followed by placebo as maintenance (n = 375). The second arm examined the addition of veliparib at 150 mg twice daily to carboplatin and paclitaxel as induction therapy followed by placebo maintenance (n = 383). In the third arm, veliparib was added at 150 mg twice daily to carboplatin and paclitaxel followed by veliparib alone at 400 mg twice daily as maintenance (n = 382).

Patient characteristics were well balanced across the arms. The median age of patients was 62 years, and approximately 60% had an ECOG performance status of 0. Two-thirds of patients had stage III disease, and most had received primary surgery, with the remaining having interval surgery. Nearly half of patients in both groups had no residual disease, and approximately 30% had residual disease.

In those testing positive for homologous recombination deficiency (HRD), the median PFS was 31.9 months in those receiving veliparib throughout the trial compared with 20.5 months in the control arm (HR, 0.57; 95% CI, 0.43-0.76; P < .001). Data were not yet sufficiently mature to conduct overall survival analyses across the groups.

In those receiving veliparib with induction chemotherapy followed by placebo maintenance, median PFS across the full study was 15.2 months versus 17.3 months in the control arm (HR, 1.07; 95% CI, 0.90-1.29). In the BRCA group, the median PFS was 21.1 months with this regimen compared with 22.0 months for the control group (HR, 1.22; 95% CI, 0.82-1.80). In the HRD-positive group, the median PFS was 18.1 months versus 20.5 months, respectively (HR, 1.10; 95% CI, 0.86-1.41).

An objective response rate (ORR) was available for patients with measurable disease at study entry (25% of study). Those receiving veliparib throughout the full study had an ORR of 84% compared with 79% and 74% in the veliparib up-front alone and control arms, respectively.

An assessment of PFS prior to maintenance therapy revealed some data on the efficacy of adding veliparib to the frontline therapy. In this analysis, PFS was not improved with the combination of veliparib and chemotherapy versus the control group (HR, 1.07; 95% CI, 0.90-1.29). These findings were consistent across subgroups.

At least 1 treatment-emergent adverse event (AE) was experienced by all patients across the 3 arms. Grade 3/4 AEs were experienced by 88% of those receiving veliparib throughout and for 88% of those receiving veliparib only in the induction combination. In the control arm, grade 3/4 AEs were experienced by 77% of patients.

The most commonly observed grade 3/4 AEs in the veliparib-throughout group compared with the control, respectively,
Apalutamid Is Linked to OS Benefit in Nonmetastatic CRPC

by GINA COLUMBUS

THE NEXT-GENERATION androgen receptor inhibitor, apalutamide (Erleada), in combination with androgen deprivation therapy (ADT) demonstrated a 25% reduction in the risk of death compared with placebo/ADT in patients with nonmetastatic castration-resistant prostate cancer (CRPC), according to updated findings of the phase III SPARTAN trial that were presented at the 2019 ESMO Congress.1,2

At a median 41 months of follow-up, results showed that the median overall survival (OS) was not reached in either arm, favoring apalutamide (HR, 0.75; 95% CI, 0.59-0.96; P = .0197). However, due to a prespecified P value boundary of .0121, these data were not found to be statistically significant.

“The P value was .0197; although close, this value was higher than the prespecified O’Brien-Fleming boundary of .0121. Accordingly, the study follow-up will continue per protocol and the final analysis will occur after 427 deaths, lead study author Matthew R. Smith, MD, PhD, director of the Genitourinary Malignancies Program at the Massachusetts General Hospital Cancer Center, stated in a presentation during the meeting. “Collectively, these results further support apalutamide as a standard-of-care option for men with high-risk, nonmetastatic castration-resistant prostate cancer.”

The FDA approved apalutamide in this setting in February 2018, based on metastasis-free survival (MFS) data from SPARTAN, which was the primary endpoint. These data showed that apalutamide reduced the risk of metastasis or death by 72% in patients with nonmetastatic CRPC. Median MFS was 40.5 months in the apalutamide arm versus 16.2 months in the placebo arm (HR, 0.28; 95% CI, 0.23-0.35; P < .0001).3

In the international SPARTAN study, researchers evaluated the safety and efficacy of apalutamide versus placebo in 1207 patients with nonmetastatic CRPC and a rapidly rising prostate-specific antigen (PSA) level, despite receiving continuous ADT. Nonmetastatic status was determined by a negative bone scan, as well as a negative CT of the pelvis, abdomen, chest, and brain. Patients were required to have a PSA doubling time of (PSADT) ≤10 months.

Patients were randomized 2:1 to receive 240 mg of apalutamide daily with ADT (n = 806) or placebo with ADT (n = 401). The average baseline PSADT was <5 months in both arms. Patients who developed

**TABLE. EFFICACY DATA BY MUTATION STATUS IN VELIA TRIAL**

<table>
<thead>
<tr>
<th>Population</th>
<th>Veliparib Throughout (n = 108)</th>
<th>Control Therapy (n = 92)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRD Population</td>
<td>34.7 (31.8-NE)</td>
<td>22.0 (17.8-29.1)</td>
<td>HR, 0.44; (0.28-0.68); P &lt; .001</td>
</tr>
<tr>
<td>BRCA Population</td>
<td>31.9 (25.8-38.0)</td>
<td>20.5 (17.8-22.8)</td>
<td>HR, 0.57; (0.43-0.76); P &lt; .001</td>
</tr>
<tr>
<td>ITT Population</td>
<td>31.9 (25.8-38.0)</td>
<td>20.5 (17.8-22.8)</td>
<td>HR, 0.57; (0.43-0.76); P &lt; .001</td>
</tr>
</tbody>
</table>

**REFERENCES**


metastases were permitted to receive abiraterone acetate (Zytiga) plus prednisone. Stratification factors also included PSADT ≥6 months or ≤6 months, use of bone-sparing agents, and N0/N1 stage disease.

The primary endpoint was MFS; secondary endpoints included time to metastasis, progression-free survival, time to symptomatic progression, and OS. For patients who developed metastases, the researchers also evaluated the time between randomization to first treatment for metastatic CRPC and subsequent progression-free survival (PFS2).

At the 20.3-month median follow-up, 61% of the apalutamide arm remained on treatment compared with 30% of the placebo group. Based on the preliminary data, an independent data monitoring committee recommended unblinding the trial and allowing patients on the placebo arm to cross over and receive open-label apalutamide (19%; n = 76), Smith said.

**SURVIVAL BENEFIT OBSERVED**

Additionally, at this first analysis, apalutamide was found to improve the time to symptomatic progression compared with placebo (HR, 0.45; 95% CI, 0.32-0.63; P < .0001). The first interim OS analysis (24% of events) revealed a trend favoring apalutamide, but data were immature. At the 2019 ESMO Congress, the updated analysis included data on OS and the effects of apalutamide on time to chemotherapy, PFS2, and safety.

OS was assessed using a preplanned group sequential testing procedure with an O’Brien-Fleming-type alpha-spending function. The second interim OS analysis was conducted following 285 OS events, which account for 67% of the required final events, with a P value boundary of .0121 for statistical significance. The study follow-up will continue per protocol, and the final OS analysis will occur after 427 events (100%), with a P value boundary of about .047, explained Smith (TIMELINE).

Additional results showed that the 4-year OS rates for the apalutamide and placebo arms were 72.1% and 64.7%, respectively. The apalutamide effect on OS was observed across patient subgroups, especially in those younger than 65 years (HR, 0.33; 95% CI, 0.14-0.74), no prior radical prostatectomy or local radiation (HR, 0.82; 95% CI, 0.60-1.11), N1 stage disease (HR, 0.52; 95% CI, 0.29-0.94), prior bone-sparing therapy (HR, 0.55; 95% CI, 0.27-1.11), and PSADT >6 months (HR, 0.57; 95% CI, 0.34-0.95). The OS benefit was also seen with apalutamide, despite patient crossover from the placebo arm.

Of those who initiated cytotoxic chemotherapy (n = 197), 115 patients were on apalutamide and 82 were on placebo. The time to initiation of chemotherapy was not reached in either arm (HR, 0.60; 95% CI, 0.45-0.80). “Per protocol sequential testing, time to initiation of chemotherapy was not formally testing for statistical significance since the OS analysis was not significant,” Smith said. “Nonetheless, it appears that apalutamide is associated with a delay in the time to initiation of chemotherapy.”

Moreover, apalutamide was also found to significantly extend PFS2 compared with placebo, with a median PFS2 of 55.5 months and 43.8 months, respectively (HR, 0.59; 95% CI, 0.45-0.68; P < .0001). Sixty-nine percent of those on the placebo arm and 40% on apalutamide received subsequent therapy, which mainly consisted of abiraterone acetate plus prednisone.

Regarding safety, apalutamide’s profile was found to be consistent with prior reports. The median duration of treatment was 31.4 months with the androgen receptor inhibitor and 11.5 months with placebo. Adverse events (AEs) were reported in 97.3% and 93.7% of apalutamide- and placebo-treated patients, respectively.Grade 3/4 AEs were reported in 53.1% of patients on the apalutamide arm and 36.7% of those on placebo, and serious AEs occurred in 33.5% and 24.9%, respectively. The treatment discontinuation rate was nearly doubled with apalutamide (13.6%) compared with placebo (7.3%). AEs that led to death occurred in 2.1% and 0.3% of patients on apalutamide and placebo, respectively.

Discontinuation due to disease progression occurred in 34% of patients in the apalutamide group compared with 74% in the placebo group, Smith explained.

Karim Fizazi, MD, PhD, head of the Department of Cancer Medicine at Institut Gustave Roussy, Villejuif, France, commented on the OS data as an invited discussant following Smith’s presentation. “It is true when you’re looking at the hazard ratio, it is 0.5, but as very honestly announced by Dr Matthew Smith, it is a very nonsignificant difference at this point. The P value is about .02 at the moment, and the boundary to claim [OS significance] is .0121. At the moment, we cannot say that apalutamide prolongs survival in this setting. [With PFS2], there is a more meaningful difference we are seeing; this is utterly important because abiraterone was provided as a potential salvage treatment in both arms. In other words, it is comparing deferred AR-targeting, at least in some patients, and at the same time, it is making a difference in [PFS2].”

In September 2019, the FDA granted a second approval to apalutamide for the treatment of patients with metastatic castration-sensitive prostate cancer.
Olaparib Doubles rPFS in Heavily Pretreated HRR-positive mCRPC

by SILAS INMAN

TREATMENT WITH THE
PARP inhibitor olaparib (Lynparza) improved radiographic progression-free survival (rPFS) compared with physician’s choice of abiraterone acetate (Zytiga) or enzalutamide (Xtandi) in men with heavily pretreated metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations, according to findings from the phase III PROfound trial presented at the ESMO Congress 2019.

The median rPFS by blinded independent review for patients with BRCA1/2 or ATM alterations (cohort A) was 7.39 months for patients treated with olaparib compared with 3.55 months for patients treated with abiraterone or enzalutamide (HR, 0.34; 95% CI, 0.25-0.47; P < .0001). The 12-month rPFS rate was 40% with olaparib and 11% for physician’s choice of therapy. Additionally, other improvements were seen in objective response rate (ORR), pain progression, and overall survival (OS), although the latter end point did not reach statistical significance due to high rates of crossover (80.6% of patients).

“PROfound is the first positive biomarker-selected phase III study evaluating a molecularly targeted therapy in men with mCRPC and highlights the importance of genomic testing in this population,” said lead investigator Maha Hussain, MBChB, of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, a Giants of Cancer Care® award winner. “Prostate cancer has lagged behind other cancers,” said Hussain. “Can suddenly see how using abiraterone or olaparib compared with 2.3% with the hormonal therapies (OR, 20.86; 95% CI, 4.18-379.18; P < .0001). The median time to pain progression was not yet reached with olaparib compared with 9.92 months for the hormonal agents, representing a 56% reduction in the risk of pain progression (HR, 0.44; 95% CI, 0.22-0.91; P = .0192). The median OS was 18.50 compared with 15.11 months, respectively (HR, 0.64; 95% CI, 0.43-0.97; P = .0173).

Although a slight trend was noted for benefit in cohort B, it was not statistically significant for rPFS nor was the magnitude as pronounced. For rPFS by blinded review, the hazard ratio in cohort B was 0.88 (95% CI, 0.58-1.36). In this cohort, the ORR was lower in the olaparib arm versus the control group (3.7% vs 9.9%).

Since the biomarkers selected were still experimental in prostate cancer, an exploratory analysis of rPFS per mutation was conducted to determine if a majority of responses occurred in a particular population. Overall, those with BRCA2 mutations had the greatest benefit in cohort A. In cohort B, those with RAD51B, RAD54L, and CDK12 had the greatest overall rPFS, although the numbers were small and preliminary.

Across both cohorts A and B, adverse events (AEs) of any grade were more commonly observed in the olaparib arm (95.3% vs 87.7%), potentially related to a significantly longer treatment duration (7.4 vs 3.9 months). Grade 3 AEs were experienced by 50.8% of patients in the olaparib arm and 37.7% in the hormonal therapy arm. “Olaparib was well tolerated, with a safety profile generally consistent with that seen in other cancers,” said Hussain.
Cabazitaxel Emerges as Third-Line Standard in Metastatic CRPC

by ONCLIVE® STAFF

MEN WHO RECEIVED cabazitaxel (Jevtana) as a third-line systemic agent for metastatic castration-resistant prostate cancer (mCRPC) had a substantial reduction in radiographic disease progression, leading to a substantial increase in overall survival (OS), the results of a randomized trial showed.1,2

The median time to progression doubled with cabazitaxel compared with abiraterone acetate (Zytiga) or enzalutamide (Xtandi), at 8.0 versus 3.7 months, respectively. After a median follow-up of 9.2 months, the median OS was 13.6 months with cabazitaxel and 11.0 months among patients who received either of the androgen-signaling inhibitors.

Men treated with cabazitaxel had significantly less pain and fewer skeletal clinical events, as reported at the 2019 ESMO Congress.

“The trial met its primary objective and reduced the risk of death by 36% versus abiraterone or enzalutamide,” said Ronald de Wit, MD, PhD, of Erasmus University Medical Center in Rotterdam, the Netherlands. “Radiographic progression-free survival [rPFS] remained superior regardless of the abiraterone/enzalutamide sequence. These results support the use of cabazitaxel over abiraterone or enzalutamide in this setting.”

The findings were published simultaneously in the New England Journal of Medicine.

Docetaxel, cabazitaxel, abiraterone, and enzalutamide have all demonstrated survival benefits in mCRPC. Study results show that patients might not respond to abiraterone after progression with enzalutamide and vice versa, said de Wit. Cabazitaxel retains activity after progression on prior docetaxel or either of the androgen-signaling inhibitors.

That background provided the rationale for the multicenter, randomized CARD trial (NCT02485691), which compared the efficacy and safety of cabazitaxel versus abiraterone or enzalutamide in men with mCRPC previously treated with docetaxel and either of the androgen-signaling inhibitors.

The principal inclusion criterion was mCRPC that progressed within 12 months on an androgen-signaling inhibitor before or after treatment with docetaxel. Investigators randomized patients to cabazitaxel plus prednisone or to abiraterone plus prednisone or enzalutamide, depending on which androgen-signaling inhibitor a patient previously received.

The primary end point was rPFS. OS was a key secondary end point, along with PFS, prostate-specific antigen (PSA) response, and tumor response. Other secondary endpoints included pain response, time to symptomatic skeletal event, safety, health-related quality of life, and biomarker analyses.

Data analysis comprised 255 randomized patients, who had a median age of 70 years. About 30% of the patients were 75 years or older. Baseline characteristics were balanced, including the sequence of prior therapies. In the cabazitaxel arm, 55.8% of patients received enzalutamide, and the majority in the control arm received abiraterone (53.2%). Median duration of prior androgen-signaling targeted therapy was 7 to 8 months.

Baseline laboratory values included median PSA of about 60 ng/mL, hemoglobin of 121 to 122 g/L, alkaline phosphatase of 122 to 132 IU/L, lactate dehydrogenase of about 250 IU/L, and neutrophil-to-lymphocyte ratio of 3.37:3.38.

The median duration of treatment was longer with cabazitaxel (22.0 vs 12.5 weeks), and median number of therapy cycles was 7 with cabazitaxel and 4 with the androgen-signaling inhibitors. More patients in the control group had at least 1 cycle of therapy with dose reduction (37.9% vs 21.4%).

Most patients in the control group discontinued treatment because of disease progression (71.0% vs 43.7%), whereas more in the cabazitaxel arm discontinued because of adverse events (AEs; 19.8% vs 8.9%), investigator decision (16.7% vs 4.0%), and patient decision (9.5% vs 3.2%).

The primary analysis showed that cabazitaxel reduced the risk of radiographic progression by 46% versus the control group (P < .0001). A preplanned subgroup analysis showed a consistent advantage for treatment with cabazitaxel.

The survival analysis showed a median OS of 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling targeted drugs. The difference translated into a hazard ratio of 0.64 (P = .0078).

CONSISTENT BENEFITS

Beyond OS, secondary endpoints consistently favored cabazitaxel:

- Confirmed PSA response: 35.7% versus 13.5% (P = .0002)
- Objective tumor response: 36.5% versus 11.5% (P = .004)
- Pain response: 45.0% vs 19.3% (P < .0001)
- Time to skeletal event: Not reached versus 16.7 months (HR, 0.59; P = .05)

Cabazitaxel-treated patients (n = 56) had improved rPFS compared with enzalutamide (n = 66), 7.4 versus 4.8 months (HR, 0.57) and with abiraterone (n = 72 versus n = 60; 8.2 vs 3.4 months; HR, 0.44).

AEs, grade ≥3 AEs, and serious AEs occurred in a similar proportion of patients in the cabazitaxel and control groups.

Invited discussant Silke Gillessen, MD, of the University of Manchester in England, described the CARD trial as well designed and addressing an unmet clinical need, with a patient population representative of patients seen in the clinic.

“The current treatment landscape is that fit patients should have docetaxel and abiraterone or enzalutamide at some stage,” she said. “A subgroup of patients can derive benefit from PARP inhibitors, and another subgroup can derive benefit from pembrolizumab. The new information provided by this trial is that cabazitaxel should be considered a new standard of care for third line [therapy] for fit patients with progressive disease on prior androgen receptor therapy in less than 12 months.”

For a full list of references, see the article at OneLive.com/link/6534.
INDICATION AND IMPORTANT SAFETY INFORMATION

**ALUNBRIG® (brigatinib)** is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. See accelerated approval information above.

**WARNINGS AND PRECAUTIONS**

**Interstitial Lung Disease (ILD)/Pneumonitis:** Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

**ALK+, anaplastic lymphoma kinase-positive; NSCLC, non-small cell lung cancer.**

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
For patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib

Think One Step Ahead WITH ALUNBRIG® (brigatinib)

Robust Overall Efficacy

<table>
<thead>
<tr>
<th>ALTA Efficacy Results</th>
<th>IRG Assessment*</th>
<th>Investigator Assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, (95% CI)</td>
<td>90 mg once daily (n=112)</td>
<td>90→180 mg once daily* (n=110)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>48% (39-58)</td>
<td>53% (43-62)</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>4 (3.6)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Duration of Response, Median in Months (95% CI)</td>
<td>13.8 (7.4-NE)</td>
<td>13.8 (9.3-NE)</td>
</tr>
</tbody>
</table>

*180 mg once daily with a 7-day lead-in at 90 mg once daily.

Systemic follow-up data (18-month median follow-up) is consistent with 8-month median follow-up.¹

ALTA Study Design: The safety and efficacy of ALUNBRIG® were evaluated in a global, two-arm, open-label, multicenter trial. The trial consisted of 222 adult patients with locally advanced or metastatic ALK+ NSCLC who had progressed on crizotinib. Patients were randomized to receive the recommended dosing regimen of 180 mg of ALUNBRIG orally once daily with a 7-day lead-in at 90 mg once daily (n=111, 18 with measurable brain metastases²), or 90 mg of ALUNBRIG orally once daily (n=112, 26 with measurable brain metastases³). The major efficacy outcome measure was confirmed objective response rate (cORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hypertension: In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

Bradycardia: Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor bradycardia and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

Visual Disturbance: In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity were reported in 7.9% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3–4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

¹Systemic follow-up data (18-month median follow-up) is consistent with 8-month median follow-up.²


Females and Males of Reproductive Potential:
Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

Creatine Phosphokinase (CPK) Elevation: In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3–4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.
Agents that cause bradycardia. When administering ALUNBRIG in combination with antihypertensive treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume treatment.

Meaningful CNS Efficacy

<table>
<thead>
<tr>
<th>Intracranial Objective Response in Patients With Measurable Brain Metastases in ALTA</th>
<th>IRC Assessment</th>
<th>Follow-Up Data (18-Month Median Follow-Up)*,†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 mg once daily (n=26)</td>
<td>90 mg once daily (n=26)</td>
</tr>
<tr>
<td>Intracranial Overall Response Rate, (95% CI)</td>
<td>42% (23-63)</td>
<td>67% (41-87)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>2 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>9 (35)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Duration of Intracranial Response, Median (months) (range)</td>
<td>NE (1.9+ - 9.2+)</td>
<td>5.6 (1.9+ - 9.2+)</td>
</tr>
</tbody>
</table>

*Median duration of follow-up was 18 months (range: 0.1-32).
†90 mg once daily with a 7-day lead-in at 90 mg once daily.
‡<90 mm in longest diameter (at baseline).

The most common serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90-180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90-180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90-180 mg group). Fatal adverse reactions occurred in 3.8% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

At the 8-month median follow-up, among the 23 patients who exhibited an intracranial response, 78% of patients in the 90-mg arm and 68% of patients in the 90-180-mg arm maintained a response for at least 4 months.

ALUNBRIG is the only ALK inhibitor with a one-tablet, once-daily recommended dosing regimen that can be taken with or without food.

Visit ALUNBRIG.com to learn more.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.8% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) in the 90 mg group were nausea (33%), fatigue (29%), headache (28%), and dyspnea (27%) and in the 90→180 mg group were nausea (40%), diarrhea (38%), fatigue (36%), cough (34%), and headache (27%).

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG.

CYP3A Inducers: Avoid concomitant use of ALUNBRIG with strong CYP3A inducers.

CYP3A Substrates: Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

Visit ALUNBRIG.com to learn more.

USE IN SPECIFIC POPULATIONS

Pregnancy: ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

Lactation: There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.

Females and Males of Reproductive Potential:

Contraception: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

Pediatric Use: The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

Geriatric Use: Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65–74 years and 4.3% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 and younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild hepatic impairment or mild or moderate renal impairment. The safety of ALUNBRIG in patients with moderate or severe hepatic impairment or severe renal impairment has not been studied.

Please see Brief Summary of the full Prescribing Information on the following pages.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

ALUNBRIG® (brigatinib) tablets, for oral use

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

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

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred in patients treated with ALUNBRIG.

In Trial ALTA (ALTa), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 5.4% of patients in the 180 mg group (180 mg once daily). In the first week of initiating ALUNBRIG, median onset was 2 days in 6.4% of patients, with Grade 3 or 4 reactions occurring in 2.7%.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drugs known to cause bradycardia is anticipated.

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia. Otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

5.2 Hypertension

In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 180 mg group. Grade 3 hypertension occurred in 1.5% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or hypertension-related decreased organ function.

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

5.3 Bradycardia

Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90–180 mg group. Grade 2 bradycardia occurred in 1.8% (9 patients) in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drugs known to cause bradycardia is anticipated. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia. Otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

5.4 Visual Disturbance

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90–180 mg group. Grade 2 bradycardia occurred in 1.8% (9 patients) in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drugs known to cause bradycardia is anticipated. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia. Otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

5.5 Creatine Phosphokinase (CPK) Elevation

Monitor patients for elevated CPK levels during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drugs known to cause CPK elevation is anticipated. For symptomatic CPK elevation, withhold ALUNBRIG and review concomitant medications for those known to cause CPK elevation. If a concomitant medication known to cause CPK elevation is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic CPK elevation. Otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic CPK elevation. Discontinue ALUNBRIG for CPK elevation that is life-threatening or otherwise uncontrolled.

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

6 ADVERSE REACTIONS

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

• Interstitial Lung Disease (ILD)/Pneumonitis

• Hypertension

• Bradycardia

• Visual Disturbance

• Creatine Phosphokinase (CPK) Elevation

• Pancreatic Enzyme Elevation

• Hyperglycemia

6.1 Clinical Trial Experience

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

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least one dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily on days 8–180 mg once daily. The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90–180 mg group. A total of 156 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to one year.

The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (68%), NSCLC adenocarcinoma histology (97%), never or former smoker (6%), ECOG Performance Status (PS) 0 or 1 (93%), and brain metastases at baseline (68%).

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90–180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall), 3.7% in the 90 mg group, and 7.3% in the 90–180 mg group) and ILD/pneumonitis (4.4% overall, 1.6% in the 90 mg group and 7.3% in the 90–180 mg group). Fetal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, and appendicitis (each 1 patient each).

In ALTA, 2.6% of patients in the 90 mg group and 8.2% of patients in the 90 mg group/7.3% in the 90–180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90 mg group) and pneumonia (1.3% in the 90–180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90–180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90–180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Table 3: Adverse Reactions in ≥ 10% (All Grades) or ≥ 3% (Grades 3-4) of Patients by Dose Group in ALTA (N=219)
5.8 Embryo-Fetal Toxicity

Decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily).

5.9 Grade 3 and 4 Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>50 mg once daily</th>
<th>90 mg once daily</th>
<th>180 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (%)</td>
<td>38</td>
<td>0.9</td>
<td>65</td>
</tr>
<tr>
<td>Hyperglycemia† (%)</td>
<td>38</td>
<td>3.7</td>
<td>49</td>
</tr>
<tr>
<td>Increased creatine kinase (%)</td>
<td>27</td>
<td>3.6</td>
<td>48</td>
</tr>
<tr>
<td>Increased lipase (%)</td>
<td>21</td>
<td>4.6</td>
<td>45</td>
</tr>
<tr>
<td>Increased alanine aminotransferase (%)</td>
<td>34</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Increased amylase (%)</td>
<td>27</td>
<td>3.7</td>
<td>38</td>
</tr>
<tr>
<td>Increased alkaline phosphatase (%)</td>
<td>15</td>
<td>0.9</td>
<td>29</td>
</tr>
<tr>
<td>Decreased phosphorus (%)</td>
<td>15</td>
<td>1.8</td>
<td>22</td>
</tr>
<tr>
<td>Prolonged activated partial thromboplastin time (%)</td>
<td>22</td>
<td>1.8</td>
<td>20</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>23</td>
<td>0.9</td>
<td>40</td>
</tr>
<tr>
<td>Lymphopenia (%)</td>
<td>19</td>
<td>2.8</td>
<td>27</td>
</tr>
</tbody>
</table>

† Includes peripheral sensory neuropathy and paresthesia

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Brigatinib Plasma Concentrations

Strong CYP3A Inhibitors

Co-administration of trizacine, a strong CYP3A inhibitor, increased brigatinib plasma concentrations and may result in increased adverse reactions. Avoid the concomitant use of strong CYP3A inhibitors with ALUNBRIG, including but not limited to certain antivirals (e.g., cobicistat, citalovir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin), antifungals (e.g., fluconazole, ketoconazole, posaconazole, voriconazole), and contraceptive. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG by approximately 50%.

7.2 Drugs That May Decrease Brigatinib Plasma Concentrations

Strong CYP3A Inducers

Co-administration of ALUNBRIG with rifampin, a strong CYP3A inducer, decreased brigatinib plasma concentrations and may result in decreased efficacy. Avoid the concomitant use of strong CYP3A inducers with ALUNBRIG, including but not limited to rifampin, carbamazepine, phenytoin, and St. John’s Wort.

7.3 Drugs That May Have Their Plasma Concentrations Altered by Brigatinib

CYP3A Substrates

Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates. Co-administration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 13.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient 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

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (complete ossification, small incisors) and visceral anomalies were observed at doses as low as 13.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forearm-hypertrophy, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestinal protruding into umbilicus), and gastruschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

ALUNBRIG can cause fetal harm.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 18.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.
Abemaciclib/Fulvestrant Improves Survival in HR+ Advanced Breast Cancer

by GINA COLUMBUS

The addition of abemaciclib to fulvestrant provided a statistically significant OS improvement in patients with hormone receptor–positive, HER2-negative advanced breast cancer who had progressed on prior endocrine therapy, according to results of the phase III MONARCH 2 trial that were presented at the 2019 ESMO Congress.

At a median follow-up of 47.7 months, the median OS with abemaciclib/fulvestrant was 46.7 months compared with 37.3 months for placebo/fulvestrant (HR, 0.757; 95% CI, 0.606-0.945; P = .0137).

The addition of abemaciclib to fulvestrant provided a statistically significant OS improvement in patients with hormone receptor–positive, HER2-negative advanced breast cancer who had progressed on prior endocrine therapy, said lead study investigator George W. Sledge Jr, MD, a 2018 Giant of Cancer Care® award winner, said at a press conference during the meeting. “This OS benefit is consistent across subgroups, including in patients with poor prognostic factors such as visceral metastasis and primary endocrine therapy resistance. Abemaciclib significantly delayed the receipt of subsequent chemotherapy in a subsequent analysis.”

The FDA approved abemaciclib in combination with fulvestrant in this patient population in September 2017, based on progression-free survival (PFS) data from the phase III MONARCH 2 study (NCT02107703). The earlier findings showed that adding abemaciclib to fulvestrant led to a 45% reduction in the risk of disease progression or death compared with fulvestrant alone.

In the MONARCH 2 trial, investigators randomized 669 pre-, peri-, or postmenopausal patients with hormone receptor–positive, HER2-negative advanced breast cancer resistant to endocrine therapy in a 2:1 ratio to receive abemaciclib/fulvestrant (n = 446) or placebo/fulvestrant (n = 223). Abemaciclib was administered at 150 mg and fulvestrant at 500 mg, both on a twice daily, continuous schedule. Enrollment occurred between August 7, 2014, and December 29, 2015.

To be eligible for enrollment on MONARCH 2, patients must have relapsed on neoadjuvant endocrine therapy on or within 1 year of endocrine treatment in the adjuvant setting, or have progressed on frontline endocrine therapy for their advanced breast cancer. No prior chemotherapy for advanced disease was permitted, and patients could not have received ≥1 line of endocrine treatment. All patients had an ECOG performance status of ≤1.

The primary end point was investigator-assessed PFS, OS was a secondary endpoint, and time to chemotherapy (TTC) was evaluated as an exploratory analysis (TABLE). Patients were stratified by site of metastasis and either primary or secondary endocrine therapy resistance. The data cutoff date was June 20, 2019.

At the median 47.7-month follow-up, 17% of patients on abemaciclib remained on treatment compared with 4% of those on placebo. The OS benefit was consistent across subgroups, including in patients with poor prognostic factors such as visceral metastasis (HR, 0.675; 95% CI, 0.511-0.891) and primary endocrine therapy resistance (HR, 0.686; 95% CI, 0.451-1.043).

Sledge, professor of medicine (oncology) at Stanford University Medical Center, also provided updated findings on PFS, with 297 events occurring on the abemaciclib arm versus 193 events on placebo. The median PFS with abemaciclib/fulvestrant and placebo/fulvestrant was 16.9 months and 9.3 months, respectively (HR, 0.536; 95% CI, 0.445-0.645; P < .0001). Moreover, the 3-year PFS rates were 29.9% and 10.1%.

The time to second disease progression also improved with the addition of abemaciclib at a median 23.1 versus 20.6 months with fulvestrant/placebo (HR, 0.675; 95% CI, 0.558-0.816). Abemaciclib/fulvestrant also showed a statistically significant improvement in median chemotherapy-free survival compared with fulvestrant/placebo, at 25.5 and 18.2 months, respectively (HR, 0.638; 95% CI, 0.527-0.773).

In the exploratory TTC analysis, abemaciclib/fulvestrant also led to a 60% delay in TTC. The median TTC was 50.2 months compared with 22.1 months in the abemaciclib/fulvestrant versus placebo/fulvestrant arms, respectively (HR, 0.625; 95% CI, 0.501-0.779; P < .0001).

**TABLE. UPDATED ANALYSIS FROM MONARCH 2**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Abemaciclib + Fulvestrant (N = 446)</th>
<th>Placebo + Fulvestrant (N = 223)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>16.9</td>
<td>9.3</td>
<td>0.536; (0.445-0.645)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>46.7</td>
<td>37.3</td>
<td>0.757; (0.606-0.945)</td>
</tr>
<tr>
<td>OS by metastatic site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral, months</td>
<td>40.3</td>
<td>32.2</td>
<td>0.675; (0.511-0.891)</td>
</tr>
<tr>
<td>Bone only, months</td>
<td>NR</td>
<td>47.3</td>
<td>0.907; (0.564-1.457)</td>
</tr>
<tr>
<td>Other, months</td>
<td>48.5</td>
<td>40.7</td>
<td>0.928; (0.528-1.632)</td>
</tr>
</tbody>
</table>

NR indicates not reached; OS, overall survival; PFS, progression-free survival.
Regarding safety, Sledge noted that the tolerability and associated adverse events (AEs) with abemaciclib were consistent with those previously reported in clinical trials. Common hematologic grade ≥3 AEs in those who received abemaciclib included neutropenia (29.9%), anemia (9.1%), and leukopenia (11.1%). There were no new cases of febrile neutropenia that were reported relative to the primary analysis (n = 6). The most frequent nonhematologic AE reported was diarrhea (14.5%); most cases of this AE occurred during the first 4 weeks of abemaciclib initiation and were effectively managed using loperamide or dose adjustments. A total 1.4% of patients discontinued treatment due to diarrhea.

Within a subset of patients who were on MONARCH 2 ≥1 year (abemaciclib [n = 240] vs placebo [n = 89]), new any-grade treatment-emergent diarrhea events that appeared after ≥1 year of therapy were reported in 28.3% and 11.2% of patients who received abemaciclib/fulvestrant and placebo/fulvestrant, respectively.

Follow-up will continue in MONARCH 2 to further characterize the OS benefit with the treatment and exploratory efficacy endpoints, Sledge concluded.

Nadia Harbeck, MD, PhD, head of the Breast Center, Ludwig Maximilians University of Munich, provided perspective on these data during the press conference.

“Fifty months to chemotherapy—this is a game changer in metastatic breast cancer. The MONARCH 2 trial shows, for the first time, a significant OS advantage in a purely second-line cohort of pre- and postmenopausal patients,” explained Harbeck. “It’s the first time we see OS data for abemaciclib, which is one of the 3 CDK4/6 inhibitors, and the delta of 10 months is really clinically meaningful. Also, [the fact that for] 46 months, patients live with their metastatic disease in the second-line [setting] with abemaciclib [is meaningful].”

Abemaciclib is also approved by the FDA for use as a single agent for patients with metastatic hormone receptor-positive/HER2-negative breast cancer who have previously received endocrine therapy and chemotherapy. The CDK4/6 inhibitor is also indicated for use in combination with an aromatase inhibitor for the frontline treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

**CDK4/6 Activity Extends to HER2+ Breast Cancer Setting**

_by ONCLIVE® STAFF_

**ADDING THE CDK4/6 INHIBITOR** abemaciclib (Verzenio) and endocrine therapy to trastuzumab (Herceptin) improved progression-free survival (PFS) in advanced hormone receptor (HR)-positive, HER2-positive breast cancer compared with trastuzumab and chemotherapy, according to findings from the randomized phase II monarcHER trial (NCT02675231).

Patients who received abemaciclib and fulvestrant (Faslodex) in addition to trastuzumab had a median PFS of 8.32 months versus 5.69 months for patients treated with the current standard of trastuzumab and chemotherapy. More than twice as many patients had objective responses with the investigational regimen as with trastuzumab and chemotherapy.

A third randomized cohort received abemaciclib and trastuzumab without fulvestrant, which led to outcomes similar to the trastuzumab-chemotherapy control group, as reported at the 2019 ESMO Congress.

“This is the first randomized study of a CDK4/6 inhibitor and endocrine therapy with trastuzumab, compared [with] chemotherapy and trastuzumab, in patients with advanced hormone receptor-positive, HER2-positive breast cancer,” said Sara Tolaney, MD, Dana-Farber Cancer Institute, in Boston, Massachusetts. “The study demonstrated that in a heavily pretreated population, the combination of abemaciclib with fulvestrant and trastuzumab led to a statistically significant improvement in both progression-free survival and the objective response rate [ORR], compared with chemotherapy and trastuzumab. There were no new safety signals identified, and generally, the regimen was well tolerated. These data suggest that abemaciclib with endocrine therapy has activity not just in patients with HR-positive, HER2-negative [disease], but also in patients with HR-positive, HER2-positive disease.”

The rationale for clinical evaluation of abemaciclib and fulvestrant in HR-positive, HER2-positive breast cancer included in vivo evidence that CDK4/6 inhibition by abemaciclib enhanced activity of HER2-directed agents. Additionally, combined inhibition of CDK4/6 and HER2 had synergistic activity in a preclinical model of resistance to HER2-directed therapies.

A phase I trial provided additional evidence that abemaciclib has clinical activity in HR-positive, HER2-positive breast cancer, reflected in an ORR of 36% and a median PFS of 7.2 months. Findings from several studies showed that adding HER2-directed therapy to endocrine therapy improved PFS in patients with HR-positive, HER2-positive advanced breast cancer, said Tolaney, associate director, Susan F. Smith Center for Women’s Cancers at Dana-Farber, and assistant professor of medicine, Harvard Medical School.

The evidence led to the development of an international, multicenter phase II randomized trial of abemaciclib and fulvestrant in pretreated HR-positive, HER2-positive advanced breast cancer. Eligible patients had received at least 2 prior HER2-directed therapies for advanced breast cancer, including required exposure to ad-trastuzumab emtansine (T-DM1; Kadcyla) and a taxane. Patients previously treated with a CDK4/6 inhibitor with fulvestrant were not eligible.

Investigators randomized 237 patients to 1 of 3 treatment regimens: abemaciclib with trastuzumab and fulvestrant; abemaciclib plus trastuzumab; and trastuzumab plus...
investigator’s choice of chemotherapy. The primary endpoint was PFS for the comparison of each of the abemaciclib arms versus the trastuzumab-chemotherapy control arm.

Tolaney said baseline characteristics were well balanced among the 3 groups, including geographic distribution (Asia/Pacific, Europe, North America, and South America), metastatic sites, prior systemic therapies, prior endocrine therapies, and prior HER2-directed therapies.

The primary analysis showed that treatment with the abemaciclib/fulvestrant/trastuzumab regimen resulted in a 37% reduction in the hazard ratio for disease progression or death versus the trastuzumab-chemotherapy arm ($P = .0506$). The abemaciclib-trastuzumab regimen led to a median PFS of 5.65 months, which did not differ from the median PFS of the control group.

Abemaciclib and fulvestrant with trastuzumab led to an ORR of 32.9% versus 16% for the other 2 groups ($P = .0042$ vs control group). Similar results emerged from an analysis limited to patients with measurable disease (36% vs 16% for the other 2 groups; $P = .0111$).

An exploratory analysis of overall survival (OS) showed an early trend in favor of both abemaciclib groups. The median OS was 24.33 months with fulvestrant, 24.07 months without fulvestrant, and 21.50 months with trastuzumab and chemotherapy. Tolaney said the final OS analysis is not expected to occur until 2021.

Overall, grade ≥3 treatment-emergent adverse events (TEAEs) occurred more often with the abemaciclib/fulvestrant/trastuzumab regimen (56.4% vs 37.7% vs 33.3%). Serious adverse events (AEs) also occurred more often with abemaciclib and fulvestrant (10.3% vs 5.2% vs 6.9%). Rates of fatal AEs and discontinuation because of AEs were similar across the 3 groups.

The most common grade ≥3 TEAEs with abemaciclib plus fulvestrant were neutropenia (26.9%), leukopenia (10.3%), thrombocytopenia (10.3%), diarrhea (9.0%), anemia (9.0%), hypokalemia (5.1%), and fatigue (3.8%).

During the discussion that followed her presentation, Tolaney was asked to speculate about whether patients treated with the triplet regimen might have done just as well with fulvestrant and trastuzumab.

The superior PFS and response rate with the triplet combination “were more likely due to synergistic activity of the 3 drugs, and I think that’s probably true for a couple of reasons,” said Tolaney. “This was a heavily pretreated population with a median of 4 prior lines of systemic therapy in the metastatic setting, and 54% of the patients had already received endocrine therapy for advanced disease. I think it’s unlikely you would have seen benefit from fulvestrant and trastuzumab. I also think the activity we’re seeing with abemaciclib-trastuzumab is really on par with chemotherapy and trastuzumab. I think the effect we’re seeing is more likely due to the additive effects and synergistic activity with the addition of fulvestrant.”

Ribociclib/Fulvestrant Combo Improves OS in Advanced HR+ Breast Cancer

by GINA COLUMBUS

Ribociclib (Kisqali) and fulvestrant (Faslodex) led to an approximate 28% reduction in the risk of death compared with placebo and fulvestrant in postmenopausal patients with hormone receptor–positive, HER2-negative advanced breast cancer, according to findings of the phase III MONALEESA-3 trial (NCT02427615) that were presented at the ESMO Congress 2019.1

The median overall survival (OS) was not reached in the ribociclib arm (42.5 months-not reached [NR]) and was 40.0 months with placebo (37.0-NR) at a median follow-up of 39.4 months (HR, 0.724; 95% CI, 0.568-0.924; $P = .00455$). The $P$ value had crossed the prespecified boundary of .0129 to claim superior efficacy, noted lead study author Dennis J. Slamon, MD, PhD.

[These data] show that there is a significant but also clinically meaningful benefit in terms of prolongation of progression-free survival [PFS] and now OS, regardless of whether the patient is premenopausal or postmenopausal and regardless of whether they received their [treatment] in the frontline setting or subsequently,” Slamon, director of clinical/translational research, Revlon/University of California, Los Angeles (UCLA) Women’s Cancer Research Program, Jonsson Comprehensive Cancer Center, and a 2014 Giants of Cancer Care® award winner, stated at a press conference during the meeting.

Ribociclib was initially approved in March
2017 for use in combination with an aromatase inhibitor (AI) for the frontline treatment of postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer.

In July 2018, the agency expanded its indication to include use in combination with an AI for pre/perimenopausal or postmenopausal women with hormone receptor–positive/HER2-negative advanced or metastatic breast cancer. It was simultaneously approved for use in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor–positive/HER2-negative advanced or metastatic breast cancer, in the frontline setting or after disease progression on endocrine therapy.

The indication to include fulvestrant was based on PFS results from the MONALEESA-3 study, in which the median PFS was 20.5 months with ribociclib and fulvestrant compared with 12.8 months for placebo/fulvestrant (HR, 0.59; 95% CI, 0.33-0.86). Additionally, median OS results with first-line ribociclib/fulvestrant were 33.6 and 19.2 months, respectively (HR, 0.546; 95% CI, 0.415-0.718). Additionally, median PFS2 was 39.8 months in the ribociclib arm versus 29.4 months in the placebo group (HR, 0.670; 95% CI, 0.542-0.830).

Moreover, no new safety signals were observed. Key grade 3/4 adverse events of special interest in the ribociclib/fulvestrant and fulvestrant/placebo arms, respectively, included neutropenia (57.1% vs 0.8%), hepatic toxicity (13.7% vs 5.8%), pulmonary disorders (0.2% vs 0%), and QTc prolongation (3.1% vs 1.2%). No grade 3/4 pneumonitis or interstitial lung disease were observed in either group, and no episodes of Torsades de Pointes were reported.

During the press conference, Nadia Harbeck, MD, PhD, head of Breast Center, Ludwig Maximilians University of Munich, discussed the clinical implications of the data.

“MONALEESA-3, for the first time, gives us data in the first- and second-line settings. For patients who have not been receiving any endocrine therapy before that, that makes it highly clinically meaningful, because we were always struggling with whether to give these drugs in the first- or second-line setting,” Harbeck explained. “Now, we see there is a first-line survival benefit; that should be the new standard of care—a CDK4/6 inhibitor in the first-line setting. The data are highly clinically meaningful, and I think they’re going to make a huge impact in how we treat metastatic breast cancer.”

CONFERENCE HIGHLIGHTS
ESMO 2019

FOR MORE VISIT: onclive.com/link/6446.
Novel Agent Shows Dramatic PFS Improvement for Heavily Pretreated GIST

by SILAS INMAN

TREATMENT WITH THE NOVEL KIT and PDGFRα inhibitor ripretinib (DCC-2618) reduced the risk of progression or death by 85% compared with placebo for heavily pretreated patients with advanced gastrointestinal stromal tumors (GISTs), according to findings from the phase III INVICTUS trial (NCT03353753) presented at the ESMO Congress 2019.

In the double-blind study, the median progression-free survival (PFS) was 6.3 months with ripretinib compared with 1.0 month for placebo (HR, 0.15; 95% CI, 0.09-0.25; P < .0001). Additionally, there was a 64% reduction in the risk of death with ripretinib compared with placebo, which was a secondary endpoint. The median overall survival (OS) was 15.1 versus 6.6 months for ripretinib and placebo, respectively (HR, 0.36; 95% CI, 0.20-0.63; P = .0004). However, the hierarchical testing procedures utilized for the study prevented a conclusive establishment of statistical significance for OS.

“Ripretinib represents a potential new standard of care with broad activity in fourth-line GIST, a patient population with advanced refractory disease and no other approved options,” said lead investigator Margaret von Mehren, MD, from Fox Chase Cancer Center. “The OS data are clinically meaningful. Patients with disease progression on placebo were allowed to cross over to receive ripretinib. Patients who crossed over had a substantial benefit in OS compared with those who did not and experienced rapid deterioration.”

Primary mutations in KIT and PDGFRα drive GISTs in approximately 85% of cases, according to von Mehren. At this time, there are no FDA-approved therapies available in the fourth-line setting following imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga). Ripretinib works as a switch-control inhibitor of KIT and PDGFRα at the juxtamembrane domain (IMD) and the main activation loop switch. The agent restores the inhibitory IMD switch, which is often deactivated in GISTs, and helps to stabilize the kinase in an inactive state.

The INVICTUS trial randomized patients in a 2:1 ratio to receive ripretinib at 150 mg daily (n = 85) or placebo (n = 44). The study was designed to assess open label ripretinib beyond progression, but findings for this arm were not presented during ESMO. The median age of patients was 60 years, with more patients aged 75 or older in the placebo group (9% vs 23%). Two-thirds of patients had received 3 prior therapies, and a third had received more than 4 (range, 4-7). The most common mutation was at KIT exon 11 (58%) followed by KIT exon 9 (16%).

The objective response rate with ripretinib was 9.4% compared with no responses in the placebo group (P = .0504). These findings were not statistically significant, which affected the ability to effectively test the significance of OS data, given the design of the INVICTUS statistical analysis. The median duration of response had not yet been reached, with 7 of 8 patients continuing to response at the time of the data cutoff of May 31, 2019.

The 6-month PFS rate was 51.0% (95% CI, 39.4%-61.4%) for the novel targeted therapy compared with 3.2% for placebo (95% CI, 0.2%-13.8%). PFS benefit was observed across all assessed patient subgroups. In those treated with 3 therapies, the hazard ratio for PFS was 0.15, in favor of ripretinib (95% CI, 0.08-0.29). In those treated with ≥4 therapies, the hazard ratio was 0.24 in favor of the switch kinase inhibitor (95% CI, 0.12-0.51).

The 6-month OS rate with ripretinib was 84.3% (95% CI, 74.5%-90.6%) compared with 55.9% for placebo (95% CI, 39.9%-69.2%).

CONTINUED ON PAGE 52 ▶
Our dedication today is to give people affected by cancer the hope of a tomorrow.

At Servier, our vision is to bring the hope of life to people affected by cancer, by dedicating everything we are into innovative therapeutic solutions. For today and tomorrow.

We work diligently to develop and deliver medicines that address critical unmet medical needs across multiple areas of oncology including:

- **Pancreatic cancer**, which causes more than 430,000 deaths a year worldwide and has five-year survival of 9%¹
- **Colorectal cancer**, which causes more than 880,000 deaths each year worldwide²
- **Acute lymphoblastic leukemia**, which affects over 56,000 adults and children a year worldwide³
- **Non-Hodgkin's Lymphoma**, which affects over 500,000 people worldwide each year⁴
- **Brain cancer**, which affects nearly 300,000 patients a year worldwide⁴
- **Gastric cancer**, which causes more than 780,000 deaths each year worldwide⁴

Our oncology medicines are available in more than 50 countries worldwide and our pipeline products demonstrates our commitment to hemato-oncology and oncology. We want our work to bring hope to patients all over the world.

---
Head & Neck Cancers

Positive ORR Findings for RET Inhibitor in Thyroid Cancer
Set the Stage for FDA Submission

by Silas Inman

The highly selective RET inhibitor selpercatinib (LOXO-292) demonstrated robust objective response rates (ORRs) for patients with RET-mutant medullary thyroid cancer (MTC) and for those with other RET fusion–positive thyroid cancers, according to findings from the phase I/II LIBRETTO-001 study (NCT03157128) presented at ESMO Congress 2019.

Findings from the trial for the first 55 patients enrolled with RET-mutant MTC who received prior treatment with cabozantinib (Caprelsa) or vandetanib (Caprelsa) will be submitted to the FDA for potential approval. Submission of the new drug application for selpercatinib is expected before the end of 2019, according to lead investigator Lori J. Wirth, MD.

In this group, which was known as the primary analysis set (PAS), the ORR was 56%, with a complete response (CR) rate of 6% and a partial response (PR) rate of 51%. Five percent of patients had developed progressive disease (PD). The median duration of response after 10.6 months of follow-up was not yet reached (95% CI, 11.1 months–not evaluable). The median follow-up for progression-free survival (PFS) was 11.1 months with a median PFS not yet reached.

“The outcomes with selpercatinib in patients with MTC who had progressed or had previous treatment on approved multikinase inhibitors (MKIs), I think, compares very favorably to MKIs when they are used in the first-line setting, and I think the drug is much less toxic,” said Wirth, from the Massachusetts General Hospital Cancer Center. “We are now initiating a randomized, global phase III trial of selpercatinib versus cabozantinib or vandetanib—investigator’s choice—in kinase inhibitor-naïve RET-mutant MTC.”

The LIBRETTO-001 trial enrolled 531 patients with various RET-altered cancers across doses of selpercatinib ranging from 20 mg/day to 240 mg twice daily. In addition to RET-mutant MTC and RET fusion–positive thyroid cancer, the trial included patients with RET fusion–positive non–small cell lung cancer, although findings for this group were reported separately. The phase II dose for the study was identified as 160 mg twice daily.

In the PAS group, the median age was 57 years, most common ECOG performance score was 1 (75%), median number of prior therapies was 2 (range, 1-8), and more than half of patients (53%) had received 2 or more MKIs.

The biochemical response rate using calcitonin levels was 91% with selpercatinib (95% CI, 80%-97%), and by carcinoembryonic antigen (CEA) levels, it was 64% with the RET inhibitor (95% CI, 50%-77%).

“The biochemical responses were deep and sustained over time,” Wirth noted. “We did see that the overall response rate, duration of response, and PFS were similar regardless of prior therapy and also similar regardless of RET mutation status, particularly M918T versus others.”

In those with RET-mutant MTC who were cabozantinib or vandetanib naïve (n = 88), the median age was 58 years and the performance scores were split between 0 (49%) and 1 (48%). The median number of prior therapies was 0, although 8% of patients had receive another MKI other than cabozantinib or vandetanib.

Of assessable patients with cabozantinib/ vandetanib-naïve RET-mutant MTC (n = 76), the ORR was 59% (95% CI, 47%-70%) and a CR rate was 1% and a PR rate of 58%. With a short duration of follow-up (5.5 months), neither duration of response nor PFS were achieved in this group. No patients had yet developed PD.

In those with RET fusion–positive MTC (n = 27), the median age of patients was 54 years. The histologies included papillary (78%), Hürthle cell (4%), poorly differentiated (11%), and anaplastic (7%). The most common ECOG performance score was 1 (59%), and the median number of prior therapies was 3 (range, 1-7). Eighty-nine percent of these patients had received prior radioactive iodine (RAI) therapy, and 70% had received systemic therapy other than RAI. Twenty-six percent had brain metastases.

Reference
von Mehren M, Attila S, Bauer S, et al. INVICTUS: a phase 3, international, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as >4th line treatment in patients with Advanced Gastrointestinal Stromal Tumor(s) (GIST) who have received treatment with prior anticancer therapies (NCT03353753). Presented at: 2019 ESMO Congress; September 27 to October 1, 2019; Barcelona, Spain. Abstract LBA97.
The ORR of 62% (95% CI, 41%-80%) consisted entirely of PRs and was seen across histologies, including those with poorly differentiated tumors. Of the 2 patients with anaplastic histology, 1 had a PR and the other had stable disease. Across the full cohort, the median duration of response after a median follow-up of 9.3 months was not yet reached. For PFS, the median follow-up was 9.9 months, and the median was not reached.

In pretreated patients with RET fusion-positive thyroid cancer (n = 26), which consisted primarily of papillary histology (78%), the ORR with selpercatinib was 62% (95% CI, 41%-80%), with no CRs. The median duration of response in this group also was not yet reached. With a median follow-up of 9.3 months, no patients developed PD.

Across all patients and doses in the LIBRETTO-001 trial (N = 531), the most common all grade treatment-related adverse events (AEs) with selpercatinib were dry mouth (27%), increased aspartate aminotransferase (AST; 22%), and increased alanine aminotransferase (ALT; 21%). The most common grade 3/4 AEs were hypertension (9%), increased ALT (7%), and increased AST (5%). The most common treatment-emergent grade 3/4 AEs were hypertension (15%), increased ALT (8%), and increased AST (7%).

Most of the AEs observed in the trial were low grade and unrelated to selpercatinib, Wirth noted. Overall, only 1.7% of patients discontinued treatment due to AEs.

“The data for selpercatinib show demonstrative efficacy and safety in both the first-line and relapsed settings. Patients with thyroid cancer have long sought targeted therapy tailored to the molecular nature of their disease, and we are hopeful that selpercatinib may be used as the standard of care in the future,” Wirth said.

In September and October of 2018, the FDA granted selpercatinib breakthrough therapy designations for all 3 indications explored in the LIBRETTO-001 trial. Under the designations, the potent RET inhibitor is eligible for an expedited review process and a rolling submission of data for a new drug application.

REFERENCE

LUNG CANCER

Durvalumab Combo Improves QOL, Reduces New Lesions in Small Cell Lung Cancer

by WAYNE KUZNAR

DURVALUMAB (IMFINZI) added to etoposide and platinum-based chemotherapy as a first-line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC) delays development of new lesions and improves patient-reported outcomes (PROs) compared with etoposide and platinum-based therapy alone, according to updated results of the CASPIAN study that were presented at the 2019 ESMO Congress.1

In addition, PD-L1 expression was found to be low in this patient setting and did not appear to be a predictive biomarker for the benefit of the durvalumab combination on clinical outcomes.

“Numerically, fewer patients developed new lesions at first progression with the combination of durvalumab plus etoposide and platinum [therapy] over the chemotherapy-alone arm, including in lung, liver, and bone [cancers], and the incidence of new brain/central nervous system [lesions] was similar between the 2 arms,” said Marina Chiara Garassino, MD, of Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy, in a presentation during the meeting.

In the phase III, global, open-label multicenter CASPIAN study (NCT03043872), 805 treatment-naïve patients with ES-SCLC were randomized 1:1 to 4 cycles of etoposide and platinum-based chemotherapy plus durvalumab at 1500 mg every 3 weeks followed by maintenance durvalumab every 4 weeks (n = 268) or up to 6 cycles of etoposide/platinum-based chemotherapy every 3 weeks plus prophylactic cranial irradiation at the investigator’s discretion (n = 269).

More than half (56.8%) of patients in the control arm received 6 cycles of etoposide/platinum treatment.

Following a preplanned interim analysis by an independent data monitoring committee, a third arm of the trial, in which patients received durvalumab, tremelimumab, and etoposide/platinum-based chemotherapy remains blinded and is continuing to final analysis.

The median age was between 62 and 63 years, about 70% of patients were male, close to 45% were current smokers, almost 47% were former smokers, and 10% had brain/central nervous system metastases. PCI was administered to 8% of patients in the chemotherapy-alone arm. Patients were stratified by whether they received carboplatin or cisplatin as their planned platinum-based agent.

Prior CASPIAN results showed that durvalumab in combination with etoposide plus either cisplatin or carboplatin in patients with treatment-naïve ES-SCLC was found to significantly improve overall survival (OS), the trial’s primary endpoint, versus chemotherapy alone without additional toxicity.

The median OS increased from 10.3 months with etoposide and platinum-based chemotherapy alone to 13.0 months with the addition of durvalumab, translating to a 27% reduction in the risk of death (HR, 0.73; 95% CI, 0.591-0.909; P = .0047) at a median follow-up of 14.2 months.2
PD-L1 is not a predictive biomarker to select patients to receive chemotherapy plus durvalumab or chemotherapy [SCLC].

—MARINA CHIARA GARASSINO, MD

In the analysis presented during the 2019 ESMO Congress, findings showed that progression patterns were similar between the 2 arms, but fewer patients in the durvalumab arm developed new lesions at first progression (41.4% vs 47.2%) of the chemotherapy-alone arm. There were also fewer new lung lesions (8.6% vs 15.2%), liver lesions (5.6% vs 8.9%), and bone metastases (4.5% vs 7.1%) in the durvalumab/chemotherapy arm.

There was a similar number of brain metastases between the durvalumab/chemotherapy and chemotherapy-alone arms (11.6% vs 11.5%) but prophylactic cranial irradiation was permitted only in the control arm, said Garassino. The rates of new lesions in regional lymph nodes were 5.6% versus 4.5%, respectively.

In terms of PD-L1 expression, Garassino said the relevance of this biomarker in SCLC and optimal cutoff must still be defined.

In CASPIAN, tumor tissue was mandated at screening if available. PD-L1 expression on immune cells and tumor cells was assessed using the Ventana PD-L1 (SP263) assay. Tumor tissue was available and tested for PD-L1 expression in 277 (51.6%) randomized patients across the durvalumab/chemotherapy and chemotherapy-alone arms. Baseline characteristics of these patients resembled those of the intent-to-treat population, and PD-L1 was analyzed as a continuous variable.

“Eighty percent of patients had negative PD-L1 on tumor cells and 58.1% on the immune cells,” said Garassino. Due to the low PD-L1 expression, a 1% cutoff was used in a post hoc analysis of OS based on PD-L1 expression. Some 5.1% of patients had PD-L1 expression ≥1% on tumor cells, and 22.4% had ≥1% PD-L1 expression on immune cells.

“PD-L1 is not a predictive biomarker to select patients to receive chemotherapy plus durvalumab or chemotherapy,” she said, as the durvalumab regimen was associated with improved OS versus etoposide/platinum without durvalumab, regardless of PD-L1 expression with a ≥1% cutoff. “No significant interaction was observed for OS and PFS and also response rate.”

Symptoms, health-related quality of life (QoL), and functioning were assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, versions QLQ-C30 and QLQ-LC13, with changes from baseline analyzed by time to deterioration per Cox proportional hazards. Time to deterioration (TTD) was defined as the time from randomization until the first clinically meaningful deterioration confirmed at the following visit or death (TABLE).

Baseline PROs scores were comparable between the experimental and control arms across all symptoms and functional domains. The durvalumab/chemotherapy combination was favored across all functioning scales. In particular, the global health status/QoL was superior with the addition of durvalumab over chemotherapy alone (HR, 0.81; 95% CI, 0.626-1.054), and the TTD of physical functioning (HR, 0.75; 95% CI, 0.581-0.970), cognitive functioning (HR, 0.61; 95% CI, 0.472-0.776), emotional functioning (HR, 0.61; 95% CI, 0.464-0.800), role functioning (HR, 0.71; 95% CI, 0.550-0.904), and social functioning (HR, 0.70; 95% CI, 0.549-0.897) favored combination treatment.

Baseline symptom scores were also comparable between arms. Durvalumab plus etoposide and platinum-based chemotherapy was favored across all symptoms collected on the QLQ-C30 and QLQ-LC13.

REFERENCES

### TABLE. TIME TO DETERIORATION FOR SELECT PATIENT-REPORTED OUTCOMES

<table>
<thead>
<tr>
<th>Patient-Reported Outcome</th>
<th>Durvalumab + Etoposide/Platinum (n = 151)</th>
<th>Etoposide/Platinum Alone (n = 126)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical, months</td>
<td>8.5</td>
<td>6.5</td>
<td>0.75 (0.581-0.970)</td>
<td>0.0276</td>
</tr>
<tr>
<td>Cognitive, months</td>
<td>8.4</td>
<td>6.0</td>
<td>0.61 (0.472-0.776)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Emotional, months</td>
<td>12.9</td>
<td>7.3</td>
<td>0.61 (0.464-0.800)</td>
<td>.0003</td>
</tr>
<tr>
<td>Key symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite loss, months</td>
<td>8.3</td>
<td>6.6</td>
<td>0.70 (0.542-0.899)</td>
<td>.0054</td>
</tr>
<tr>
<td>Fatigue, months</td>
<td>5.5</td>
<td>4.3</td>
<td>0.82 (0.653-1.027)</td>
<td>.0835</td>
</tr>
<tr>
<td>Chest pain, months</td>
<td>10.6</td>
<td>7.8</td>
<td>0.76 (0.575-0.996)</td>
<td>.0464</td>
</tr>
</tbody>
</table>
EOMO Data Show More Can be Done for Cancer of Unknown Primary Patients

Two research papers presented by Roche and Foundation Medicine at the 2019 European Society of Medical Oncology (ESMO) Annual Meeting demonstrate both the promise of an innovative precision medicine driven clinical trial (CUPISCO) for patients with cancer of unknown primary (CUP), as well as the challenges of identifying eligible patients for the trial, according to ESMO guidelines.1,2 CUP represents 3-5% of all cancer diagnoses.3 By definition, patients diagnosed with CUP have metastatic disease, but the specific site of the primary cancer is unknown. Consequently, traditional treatment approaches, which rely on the site of origin being known, are often ineffective. The most common treatment for CUP - six rounds of platinum-based chemotherapy - results in a median overall survival rate of less than one year.4

The CUPISCO study [NCT03498521], a randomised, prospective phase II clinical trial, seeks to discover whether a better treatment for CUP might exist by comparing the efficacy and safety of molecularly guided therapy (MGT) or cancer immunotherapy, versus standard chemotherapy. The CUPISCO study builds upon prior research by Foundation Medicine, which used comprehensive genomic profiling (CGP) to identify genomic alterations in CUP patients for which targeted treatments could be applied.3

In the first paper presented at ESMO this year, a retrospective analysis of 303 CUP patients revealed that 32% would have been potentially eligible for the molecularly guided targeted or immunotherapy treatment options in CUPISCO, because they exhibited a genomic alteration for which an alternative treatment may be effective. To make that determination, archival tissue from centrally reviewed CUP cases was subjected to CGP using the FoundationOne® CDx test.1

“The CUPISCO trial offers doctors the opportunity to explore new treatment approaches that are based on the specific tumour mutation rather than relying solely on the site of origin - a real game-changer for CUP patients,” said Prof. Alwin Krämer, Head of Clinical Cooperation Unit Molecular Hematology/Oncology, and the CUP-syndrome task force, German Cancer Research Center (DKFZ), National Center for Tumor Diseases (NCT) and Department of Internal Medicine, University of Heidelberg, Germany.

Comprehensive genomic profiling is a tumour testing method in a large set of cancer-related genes (which can cover hundreds of genes in one test) that detects both known and novel variants across the four main classes of genomic alterations.

It can also identify genomic signatures such as tumour mutational burden or microsatellite instability. It is a pan-tumour approach that can be applied across any type of cancer.6,7,8,9,10

But as promising as these findings are, a second paper presented at the congress reveals challenges in identifying and enrolling patients onto the study, who belong to the ‘poor risk prognosis’ subset of CUP, as defined by ESMO guidelines. This research outlined the barriers to enrolling patients according to standardised screening and diagnostic processes. As of 19 March 2019, 157 patients had been screened for the study, which is currently recruiting histologically confirmed poor risk CUP patients. Using ESMO guidelines, 91 of those patients, or 58%, failed the screening process, for reasons such as issues in identifying this subset of CUP patients, insufficient quality or quantity of tissue available for diagnostic workup or sequencing and the declining health of individuals due in part to delays from referral centres.2

This high screening failure rate highlights the difficulties inherent in making accurate diagnoses of poor risk CUP, and suggests that more support is needed for oncologists when it comes to rare cancers of this nature.

Prof. Krämer added, “We need a robust interconnected network that links referral centres to relevant clinical trial sites so that patients in critical conditions can gain access earlier to potentially life-saving trials.”

To date, over 140 CUP patients have already enrolled in the CUPISCO trial and recruitment is ongoing in more than 30 countries across Europe, as well as Latin America, Australia, and South Korea. In all, approximately 800 patients will be enrolled.3 Although ongoing, the CUPISCO approach is already informing clinical practice. By seeking to connect insights of a patient’s tumour profile using CGP with a dedicated decision making process for individual patients, physicians are being equipped with vital intelligence on what drives the growth of cancer – helping to drive understanding of how to diagnose and treat all types of cancer including CUP.

REFERENCES
Investigators Link Novel Biomarker to Therapy in DLBCL Trial

by RACHEL NAROZNIAK, MA

INVESTIGATORS ARE EXPLORING the novel genetic biomarker Denovo Genomic Marker 1 (DGM1) as a potential predictor of benefit from the experimental agent enzastaurin in treatment-naïve patients with high-risk diffuse large B-cell lymphoma (DLBCL), the most common non-Hodgkin lymphoma subtype.1

DGM1 is a polymorphism on chromosome 8.2 Encouraged by evidence that DGM1 positivity is predictive for efficacy with enzastaurin, investigators are evaluating the agent in the phase III ENGINE trial (NCT03263026).3

The study is designed to enroll 235 patients with CD20-positive DLBCL and randomize them to standard-of-care (SOC) rituximab (Rituxan) with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) alone or enzastaurin or R-CHOP alone for 6 cycles during the combination phase (FIGURE). The study’s primary endpoint is overall survival (OS) in patients with DLBCL who test positive for DGM1, and the secondary endpoint is OS in those without the genetic polymorphism. ENGINE’s investigators hope to discover whether enzastaurin combined with R-CHOP is a more efficacious frontline option than R-CHOP alone, as well as whether DGM1’s presence correlates with response to enzastaurin in this setting.3

Enzastaurin inhibits protein kinase C (PKC) β, an enzyme that promotes angiogenesis and thereby retards tumor growth.3 The PKCβ inhibitor has been tested in DLBCL in 2 previous trials, among more than 60 trials overall. The phase III PRELUDE study (NCT00332202) compared the agent with placebo in high-risk DLBCL. No difference was found in 4-year disease-free survival (70% vs 71%) or OS (81% vs 82%) between the enzastaurin and placebo arms. The phase II S028 trial (NCT00451178) evaluated enzastaurin in combination with R-CHOP versus R-CHOP in the frontline setting for those with intermediate/high-risk disease. “Both studies failed to demonstrate any significant benefit [associated with] the addition of enzastaurin,” said Owen O’Connor, MD, PhD, an ENGINE investigator and director of the Center for Lymphoid Malignancies in the Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center in New York, New York.

Multiple trials have failed to improve on R-CHOP by combining it with other agents, he noted. “Efforts to improve the care of patients with DLBCL have for the most part focused on CHOP or R-CHOP–plus studies, [but] over the last 10 to 15 years, all of these studies have been negative; all have failed to show that adding 1 more drug to R-CHOP produces positive changes in outcome.” O’Connor cited the ROBUST (NCT02285062) and PHOENIX (NCT01855750) studies as recent examples of unfruitful attempts to yield a new R-CHOP-plus regimen in DLBCL. ROBUST was notably the first trial to compare lenalidomide (Revlimid) with R-CHOP (R²-CHOP) to R-CHOP alone in treatment-naïve patients with CD20-positive activated B-cell-like DLBCL. Earlier phase II studies had suggested that this experimental combination might offset the poor prognosis inherent in the ABC phenotype.4 PHOENIX tested the combination of ibrutinib (Imbruvica) and R-CHOP with R-CHOP in patients with untreated non-germinal center B-cell DLBCL, including patients with the ABC subtype.5

Neither lenalidomide nor ibrutinib added to R-CHOP in either study extended survival: ROBUST did not meet its primary end point of progression-free survival, and PHOENIX missed its primary end point of event-free survival.4,5 However, positive trends with R²-CHOP were noted in subgroups with high-risk and advanced stage DLBCL.

PHASE III ENGINE TRIAL

RANDOMIZATION: 1:1
N = 235

Eligibility criteria
• ≥18 years of age
• CD20+ DLBCL based on WHO classification and confirmed at enrolling site
• ECOG performance status of 0, 1, or 2
• IPI score ≥3
• Left ventricular ejection fraction ≥50% by echocardiography or nuclear medicine multigated scan
• Has available presystemic treatment DLBCL tumor biopsy tissue/slides for central pathology review

AEs indicates adverse events; DGM1, Denovo Genomic Marker 1; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; WHO, World Health Organization.

FIGURE. ENZASTAURIN WITH R-CHOP IN DGM1-POSITIVE DLBCL

Experimental arm: R-CHOP and enzastaurin
Control arm: R-CHOP and placebo

End Points:
Primary OS in patients with DGM1 biomarker
Secondary OS in patients without DGM1 biomarker, AEs

CONTINUED ON PAGE 58
Join the OncLive® community to create solutions in healthcare through interactions with your peers.

A network of information awaits.

**Collaborate.** Share thoughts and case examples with fellow oncology professionals through live discussions hosted by OncLive®.

**Network.** Reconnect with peers in the community, and meet new professionals to expand your network.

**Debate.** Weigh the pros and cons of new treatment options, examine healthcare costs, and delve into the latest health tech trends.

Community.OncLive.com
and has been implicated in the biology of DLBCL, but the relationship of that transcription factor is not clear," O'Connor said. Investigators hope that ENGINE will further elucidate DGM1's role in DLBCL.

ENGINE's biomarker-driven design distinguishes it from PRELUDE and S028, as well as from other clinical trials in DLBCL, O'Connor said.

“What is different about ENGINE is [that] the founders have massive expertise in genetic profiling and bioinformatics and have spent a lot of time trying to identify potential biomarkers predictive of benefit,” he said. “Our platform is not simply going to be doing these big, randomized phase III trials and hoping that the addition of some new drug to R-CHOP is going to be positive.”

Although insight from the genomic screening of PRELUDE and S028 patient data has given investigators compelling reasons to hypothesize that enzastaurin will be efficacious in the DGM1-positive patient subgroup, the decision to jointly administer the agent with standard R-CHOP has less supportive clinical evidence.

“There are really no hardcore data that have systematically established synergy between enzastaurin and R-CHOP; [ENGINE is] mostly predicated on a far more rudimentary assumption, which is [that] if enzastaurin is active in large cell lymphoma and affects biology known to be important in large cell lymphoma, then adding it to an SOC regimen in large cell lymphoma should produce some benefit," O'Connor said.

Enzastaurin’s mechanism of action and the extent of the agent’s synergy with R-CHOP are key foci of ENGINE investigators, who will conduct a response assessment and unblind each subject’s treatment assignment once the combination phase concludes.3 Those who have a complete or partial response with the combination therapy will be offered subsequent single-agent enzastaurin for up to 2 years.

Enzastaurin was originally developed by Eli Lilly. Denovo Biopharma, which acquired worldwide rights to the agent, said the drug did not demonstrate sufficient efficacy in the clinical trials in which it was originally tested, but that the company used its biomarker platform to identify DGM1 as a promising marker. ENGINE is currently active at 51 sites across the United States and China.6

REFERENCES
ALL PARP INHIBITORS ARE NOT THE SAME\(^1-3\)

ZEJULA is the only PARP inhibitor evaluated in a Phase 3 trial that isolated the gBRCA\(^{mut}\) and non-gBRCA\(^{mut}\) cohorts\(^4-6\)

**gBRCA\(^{mut}\)**

<table>
<thead>
<tr>
<th>MONTHS ZEJULA</th>
<th>VS</th>
<th>MONTHS Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td></td>
<td>5.5</td>
</tr>
</tbody>
</table>

Median PFS

HR=0.26; 95% CI, 0.17-0.41, P<0.0001

**non-gBRCA\(^{mut}\)**

<table>
<thead>
<tr>
<th>MONTHS ZEJULA</th>
<th>VS</th>
<th>MONTHS Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.3</td>
<td></td>
<td>3.9</td>
</tr>
</tbody>
</table>

Median PFS

HR=0.45; 95% CI, 0.34-0.61, P<0.0001

**Study design:** NOVA, a Phase 3, double-blind, placebo-controlled trial, evaluated the safety and efficacy of ZEJULA in women (N=553) with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to second-line or later platinum-based chemotherapy. Patients were randomized to receive ZEJULA or placebo once daily. The primary end point was PFS as assessed by an independent review. NOVA separately evaluated PFS in both the gBRCA\(^{mut}\) and non-gBRCA\(^{mut}\) cohorts. PFS was measured from time of randomization to time of disease progression or death.\(^1,4\)

**Important Safety Information**

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 1.4% of patients receiving ZEJULA vs 1.1% of patients receiving placebo in Trial 1 (NOVA), and 0.9% of patients treated with ZEJULA in all clinical studies. The duration of ZEJULA treatment in patients prior to developing MDS/AML varied from <1 month to 2 years. All patients had received prior chemotherapy with platinum and some had also received other DNA damaging agents and radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. Grade 3-4 thrombocytopenia, anemia and neutropenia were reported in 29%, 25%, and 20% of patients receiving ZEJULA, respectively. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, in 3%, 1%, and 2% of patients, respectively. 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 of treatment, 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. Grade 3-4 hypertension occurred in <1% of patients. Monitor blood pressure and heart rate 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. 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. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

In clinical studies, the most common adverse reactions (Grades 1-4) in ≥10% of patients included: thrombocytopenia (61%), anemia (50%), neutropenia (30%), leukopenia (17%), palpitations (10%), nausea (74%), constipation (46%), vomiting (34%), abdominal pain/distention (33%), mucositis/stomatitis (20%), diarrhea (20%), dyspepsia (18%), dry mouth (10%), fatigue/asthenia (57%), decreased appetite (25%), urinary tract infection (13%), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation (10%), myalgia (19%), back pain (18%), arthralgia (13%), headache (26%), dizziness (18%), dysgeusia (10%), insomnia (27%), anxiety (11%), nasopharyngitis (23%), dyspnea (20%), cough (15%), rash (21%) and hypertension (20%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients included: decrease in hemoglobin (85%), decrease in platelet count (72%), decrease in white blood cell count (66%), decrease in absolute neutrophil count (53%), increase in AST (36%) and increase in ALT (28%).

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

These highlights do not include all the information needed to use ZEJULA® safely and effectively. See full prescribing information for ZEJULA available at www.ZEJULA.com.

**ZEJULA® (niraparib) capsules**

**INDICATIONS AND USAGE**

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.

**DOSAGE AND ADMINISTRATION**

**Recommended Dosage**

The recommended dose of ZEJULA as monotherapy is 300 mg (three 100 mg capsules) taken orally once daily.

**Dose Adjustments for Adverse Reactions**

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Tables 1, 2, and 3.

**Table 1: Recommended dose modifications for adverse reactions**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>300 mg/day (three 100 mg capsules)</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>200 mg/day (two 100 mg capsules)</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>100 mg/day* (one 100 mg capsule)</td>
</tr>
</tbody>
</table>

*If further dose reduction below 100 mg/day is required, discontinue ZEJULA.

**Table 2: Dose modifications for non-hematologic adverse reactions**

<table>
<thead>
<tr>
<th>Non-hematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment</th>
<th>Dose modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction.</td>
<td>Discontinue medication.</td>
</tr>
<tr>
<td>Resume ZEJULA at a reduced dose per Table 1. Up to 2 dose reductions are permitted.</td>
<td></td>
</tr>
</tbody>
</table>

*CTCAE=Common Terminology Criteria for Adverse Events

**Table 3: Dose modifications for hematologic adverse reactions**

<table>
<thead>
<tr>
<th>Platelet count &lt;100,000/μL</th>
<th>Hematologic adverse reaction requiring transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>First occurrence:</td>
<td>Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL.</td>
</tr>
<tr>
<td></td>
<td>Resume ZEJULA at same or reduced dose per Table 1.</td>
</tr>
<tr>
<td></td>
<td>If platelet count is &lt;75,000/μL, resume at a reduced dose.</td>
</tr>
<tr>
<td>Second occurrence:</td>
<td>Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL.</td>
</tr>
<tr>
<td></td>
<td>Resume ZEJULA at a reduced dose per Table 1.</td>
</tr>
<tr>
<td></td>
<td>Discontinue ZEJULA if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.*</td>
</tr>
</tbody>
</table>

*If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue ZEJULA (see Warnings and Precautions).

**Table 4: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA**

<table>
<thead>
<tr>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10</td>
</tr>
</tbody>
</table>

**Cardiovascular Effects**

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA. Grade 3-4 hypertension occurred in 9% of ZEJULA treated patients compared to 2% of placebo treated patients in Trial 1. Discontinuation due to hypertension occurred in 1% of patients. Monitor blood pressure and heart rate monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary (see Dosage and Administration).

**Embryo-Fetal Toxicity**

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman. 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). Due to the potential risk to a fetus, ZEJULA should be used only when potential benefits outweigh potential risks to the fetus. See Warnings and Precautions for the discussion of potential benefits and risks for the pregnant woman. See Warnings and Precautions for a discussion of potential benefits and risks for the pregnant woman.

**Clinical Trials Experience**

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

The safety of ZEJULA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in Trial 1 (NOVA). Adverse reactions in Trial 1 led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (29%). The permanent discontinuation rate due to adverse reactions in Trial 1 was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 4 and Table 5 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA.

**CONTRAINdications**

None.
The following adverse reactions and laboratory abnormalities have been identified in ≤1% to ≤10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table. tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, epistaxis.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women. 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 embry-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see Warnings and Precautions]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus.

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

**Lactation**

**Risk Summary**

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

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

**Females and Males of Reproductive Potential**

**Pregnancy Testing**

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

A pregnancy test is recommended for females of reproductive potential prior to initiating ZEJULA treatment.

**Contraception**

Females

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

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.

**Pediatric Use**

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

**Geriatric Use**

In Trial 1 (NOVA), 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

**Renal Impairment**

No dose adjustment is necessary for patients with mild (CrCl 50 to 89 mL/min) to moderate (CrCl ≥ 29 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance estimated as the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

**Hepatic Impairment**

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-O DVW) criteria. The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown.

**OVERDOSAGE**

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

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling.

**REFERENCES**

CLINICAL PERSPECTIVES

LUNG CANCER

Rising Incidence of Fatty Liver Disease Holds Implications for Trends in HCC

by DANIELLE TERNYILA

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD), a risk factor linked to the development of hepatocellular carcinoma (HCC) and increased mortality, is growing in clinical significance, according to Katherine A. McGlynn, PhD, MPH.

McGlynn and colleagues studied data from patients who underwent an abdominal ultrasound in the Third National Health and Nutrition Examination Survey (NHANES III) study between 1988 and 1994. This allowed for 21 to 27 years of follow-up of mortality after the initial ultrasound.

NAFLD was seen in 33% of the patients examined in this analysis (35% of males and 31% of females). Additionally, NAFLD was seen more commonly in Mexican Americans; about 40% had NAFLD compared with 32% of Caucasians and 29% of African Americans. Age also appeared to play a role in the development of NAFLD, because about 40% of patients 50 years and over had NAFLD compared with 20% of those younger than 50 years.

About one-third of deaths in the patients studied were caused by cardiovascular disease, with cancer—notably HCC—as the second leading cause. Other risk factors that played a role in mortality among these patients included excessive alcohol consumption, smoking, and obesity.

McGlynn presented the findings at the 2019 International Liver Cancer Association Annual Conference.

In an interview with OncologyLive®, McGlynn, senior investigator in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute, discussed the population attributable fraction of NAFLD in developing HCC, as well as related disorders, in the United States that contribute to mortality risk.

Q: Could you provide the rationale for population analysis of patients with HCC?

We [looked at] rates of HCC around the world and in the United States. Rates in the United States may have plateaued and started to decline, which is very good news. However, several years ago when we started studying why rates were going up, we calculated population attributable fractions, which we did for all of the risk factors that we could [measure] using data from the SEER [Surveillance, Epidemiology, and End Results] Medicare Program. The cancer diagnosis comes from SEER, the data come from Medicare, and this gives you a good idea of what contributions the risk factors make.

We calculated odds ratio, and using [those] and prevalence of the population, we calculated population attributable risks for the risk factors. We found that although hepatitis C virus (HCV) and hepatitis B virus (HBV) have, by far, the biggest odds ratios [for developing HCC], and they are the biggest risk to the individual themselves, on a population basis, the metabolic disorders and NAFLD make a much bigger contribution because they are much more common in the population.

We also looked at the contribution of NAFLD to overall mortality in the population because if you’re just concentrating on HCC, that is a fairly rare outcome, but in terms of total population mortality [it was a significant contribution]. We used data from the NHANES III population to look at risk of mortality among people who had NAFLD and among people who did not. We found a significantly increased risk of mortality in people who have NAFLD, and a significantly increased risk of diabetes mortality. Among men, there was also a significantly increased risk in liver disease mortality.

I think those are very important findings and will need to be followed because, unfortunately, the risk of NAFLD is increasing in the population [as] obesity[rates rise].

Q: What do you think is contributing to the decline in HCC in the United States?

We are not entirely sure, but it could be that HCV as a risk factor is diminishing now, although the rate of decline started around 2012. That was before any of the direct-acting antivirals were able to have a big effect in the population. We are not entirely sure what’s going on because the percentage of the population that was supposed to [be affected by] the big HCV effect were the Baby Boomers born between 1945 and 1965. The projections [regarding] the Baby Boomers and HCC were based on them having a big risk of HCC over time. However, the decline started happening when the average Baby Boomer was 57 years old, which is before the [mean] age of HCC [onset].

In the population, the mean age of HCC [onset] in men is about 62 years and in women it’s about 68 years. Having this peak out when Baby Boomers [reached age] 57 was a little unexpected, but it could be...
that [those with] HCV are just doing better. Treating HBV probably has very little effect because HBV is a much less significant risk factor in the population, so we are not quite sure what’s going on yet.

**Q:** What risk factors did you look at?

We looked at HCV, obviously, which was long thought to be a driving risk in the United States. We [also] looked at HBV, excessive alcohol consumption, smoking to some extent, rare genetic disorders, and the metabolic disorders.

We found that, obviously, the biggest increased risk to the person was HCV—about a 50-fold increased risk of developing HCC if you have an HCV infection. With HBV, the risk was about 18-fold or higher. The genetic disorders and alcohol consumption were about a 7-fold increased risk.

The metabolic disorders, comparatively, were about a 3-fold increased risk, so you might think by looking at that, metabolic disorders aren’t contributing much, but you have to keep in mind that when you calculate odds ratios, you’re talking about the risk in a person who has that risk factor. It’s not a population perspective, really. It’s just if you have a particular risk factor.

What we did then to calculate the population’s attributable risk is take into account both the odds of developing HCC and the prevalence in the population. Once you do that, metabolic disorders rise to the top; about 35% of tumors were related to the metabolic disorders, including NAFLD-impaired, fasting-glucose, metabolic syndrome. We also got medical codes for obesity and diabetes in there. It was basically any of this whole group of disorders that are very highly correlated, so 35% of tumors in the population related to those [disorders] is fairly impressive.

HCV was second, in about 20% of tumors, and then, as you went down, fewer and fewer percentages of tumors were related. HBV was only about 4%, for example. Of course, they differed by sex, race, and ethnicity. HCV had a much bigger effect in blacks. The metabolic disorders have a bigger effect in whites and Hispanics. It’s always good to keep in mind that we are a multiracial, multiethnic population, so you have to account for differences. Also, there were differences by sex.

**Q:** Could you discuss the risk of mortality in these patients?

As I mentioned, [these calculations were made with data from] the NHANES III study. NHANES III is a cross-sectional study of the population that is going on in the United States somewhere all the time. We used data from the [portion of the] NHANES III that took place between 1988 and 1994. We wanted to use that particular version of it because abdominal ultrasound was done for the adults during that part of the study, and you get a much better feel for NAFLD using abdominal ultrasound than you do using any of these indices, which rely on the combination of factors like liver enzymes and so on.

The other reason we wanted to use NHANES III was that it gave sufficient time for mortality events to occur. [If patients] were enrolled between 1988 and 1994, we had about 21 to 27 years of follow-up. Some other analyses that had been done were done after [about] 10 years of follow-up, which is insufficient time for deaths [to occur].

In the population, what we found was that about 32% to 33% of the population had NAFLD, which is a little bit higher than you’ve heard from some other [data] coming out. [This estimate, however,] was based on ultrasound, so I think it is accurate. NAFLD was more common among males; [it was found in] about 35% of males and 31% of females. So overall, it was more like 32% to 33%.

It was higher in Mexican Americans, which has been widely reported previously, at about 40%. [It was found in] about 32% of whites and again, as has been reported, in a lower percentage among blacks, around 29%. It was also higher with age: By the time you got to 50 years and over, about 40% of the population had NAFLD, versus 20% in younger patients.

We took those outcomes and we looked at the deaths and causes of death. About a third occurred among the individuals with NAFLD. More than a third of those were due to cardiovascular disease, which, again, was not a surprise because it was previously reported. Cancers were next, [followed by] deaths from liver disease, kidney disease, and diabetes. Of these, the ones that were significantly higher among individuals with NAFLD were all-cause mortality with about a 20% increased risk in diabetes mortality, which was about a 225% increased risk of death.

If you then calculate the population attributable fraction, it turns out that about 7.5% of people who die in the United States, have NAFLD-related mortality—at least in 2015. That doesn’t sound huge; it was about 200,000 of about 2.7 million deaths that year.

However, if you look at some other risk factors, it puts it into perspective because smoking accounts for anywhere between 18% and 25% of deaths. Obesity is probably around 18%, and that is, of course, a co-traveler with NAFLD. Alcohol is lower, at around 2% to 6%. Smoking is going down in the population, so in terms of being a major risk factor contributing to death, smoking, hopefully, will become less and less of a factor.

Unfortunately, obesity and, as a result, NAFLD, are increasing. [We thought] the latest data from NHANES III [would] show that the obesity epidemic had leveled off in the United States, but according to these data, it has unfortunately not. It’s gone up again. I think it’s a real problem, and one that needs to be taken seriously.

**Q:** What does this analysis highlight about the future of patients with NAFLD?

We were surprised to see that while [HCC] rates may be going down, they may again level off because HCV can run a much higher risk to the person. So, if you have had HCV, your likelihood of developing HCC is great. That may have contributed to this big rise. Maybe what we are seeing is just a leveling off, and we will see it plateauing with NAFLD because NAFLD does not, by any stretch, have the same effect that HCV does. However, we all recognize with NAFLD that the biggest risk is not in developing HCC; it’s in developing cardiovascular disease. Cardiovascular disease rates have been going down in the United States for many years, so hopefully this is not going to bring them back up again.
Novel Induction Regimens Boost Outcomes in Myeloma

by KRISTI ROSA

THE GOAL OF INDUCTION regimens for patients with newly diagnosed multiple myeloma is to reduce the burden of disease and prolong durability of response and overall survival, while minimizing toxicity, Saad Z. Usmani, MD, said during a presentation at the inaugural Charlotte Plasma Cell Disorder Congress.

“Picking therapies and then adjusting doses or stopping therapy as needed are extremely important,” added Usmani, chief of the Plasma Cell Disorders Program and director of clinical research in hematology, chief of the Plasma Cell Disorders Program and director of clinical research in hemato - logic malignancies at Levine Cancer Institute of the Carolinas Medical Center in Charlotte, North Carolina. “Recognizing that patients are developing adverse events [AEs] from therapy early and then intervening are also essential.”

Triplet combinations are considered optimal for treating patients with newly diagnosed multiple myeloma (FIGURE). The combination of lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVd) is the most commonly used regimen, whereas the triplet of carfilzomib (Kyprolis), lenalidomide, and dexamethasone (KRd) is known to induce deep responses, Usmani said. For certain patients, such as those with renal failure, the combination of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is preferred, he added. Moreover, the regimen of ixazomib (Ninlaro), lenalidomide, and dexamethasone is being explored in clinical studies.

DEEP RESPONSES OBSERVED WITH CHEMOTHERAPY COMBINATIONS

The phase III SWOG-S0777 trial randomized patients with newly diagnosed disease 1:1 to receive initial treatment with either RVd (n = 242) or lenalidomide and dexamethasone (Rd) alone (n = 229), both followed by Rd maintenance. Results showed that the median progression-free survival (PFS) was 43 months in patients who received RVd versus 30 months in those who received Rd alone (HR, 0.712; P = .002).

“This trial only validated what we were already practicing in the United States,” Usmani said. “We were already [using] RVd as induction therapy.”

The oral proteasome inhibitor ixazomib was also evaluated in combination with lenalidomide and dexamethasone in an open-label phase I/II trial. In 64 treatment-naive patients with newly diagnosed disease, the overall response rate (ORR) observed with the triplet was 92%.

“When we’re thinking about different proteasome inhibitors partnered with lenalidomide/dexamethasone, it will come down to how good that deep response is,” Usmani said. “However, if the [data from the] phase III trials hold true, this will be a reasonable combination option for induction.”

In the small phase II Intergroupe Francophone du Myélome (IFM) study, investigators looked at the safety and efficacy of 4 cycles of KRd followed by autologous stem cell transplant (ASCT) then consolidation with KRd for 4 cycles and lenalidomide maintenance in patients with newly diagnosed disease. The combination was associated with a 2-year PFS rate of 91% and a robust depth of response: 70% of patients achieved minimal residual disease (MRD) negativity after consolidation. However, 17% of patients experienced cardiac and vascular AEs; as such, cardiac toxicity is a concern with this regimen, Usmani said.

ASCT IN THE ERA OF NOVEL AGENTS

With the addition of several multiagent regimens, ASCT continues to provide benefit in the multiple myeloma space, Usmani said (TABLE). In the 2009 IFM study, patients 65 years or younger with newly diagnosed disease received RVd for 3 cycles and then underwent stem cell collection. Participants in the transplant arm (n = 350) then received melphalan at 200 mg/m\(^2\) and ASCT followed by RVd consolidation for 2 cycles followed by lenalidomide maintenance, whereas patients in the nontransplant arm (n = 350) received RVd for 3 more cycles followed by lenalidomide maintenance. The median PFS in the ASCT arm was 50 months, whereas it was 36 months in the no-transplant arm (P < .001). Although these results are promising, more data are needed to validate the role of early transplantation in multiple myeloma, Usmani said.

ASCT With RVd

In the 2009 IFM study, patients 65 years or younger with newly diagnosed disease received RVd for 3 cycles and then underwent stem cell collection. Participants in the transplant arm (n = 350) then received melphalan at 200 mg/m\(^2\) and ASCT followed by RVd consolidation for 2 cycles followed by lenalidomide maintenance, whereas patients in the nontransplant arm (n = 350) received RVd for 3 more cycles followed by lenalidomide maintenance. The median PFS in the ASCT arm was 50 months, whereas it was 36 months in the no-transplant arm (P < .001). Although these results are promising, more data are needed to validate the role of early transplantation in multiple myeloma, Usmani said.

ASCT With KRd

To evaluate the role of ASCT with KRd, investigators evaluated data from a phase I/II trial in which KRd induction was followed by randomization to either ASCT or no ASCT followed by KRd consolidation for 4 cycles and KRd maintenance for 10 cycles. Results showed that KRd plus ASCT resulted in a 3-year PFS rate of 86% versus 80% with KRd alone.

“The bottom line for this particular study was that additional ASCT to the schema deepens the response in terms of MRD negativity,” Usmani said. “It improves 3-year PFS as well.”
**MONOCLONAL ANTIBODIES GENERATE EXCITEMENT**

Monoclonal antibodies have a novel mechanism of action that allows for additive or synergistic effects with current agents, they are generally well tolerated, and they can be combined with other immunotherapies.

“We are all excited about monoclonal antibodies because they can be [used] with existing regimens without adding a lot of toxicity,” Usmani said. “They do not have overlapping AEs [adverse events] and they can be [used] to target the bone marrow microenvironment, cancer cells, and immune signals.”

The GRIFFIN trial is comparing daratumumab (Darzalex) plus bortezomib, lenalidomide, and dexamethasone (D-RVd) to RVd alone in patients with newly diagnosed disease who are eligible for high-dose therapy and ASCT.7 The primary aim of the trial is to evaluate dose-limiting toxicities during 1 cycle of D-RVd, Usmani said.

The quadruplet regimen was tolerable, depth of response to the combination deepened during maintenance, and ORR improved over time. Updated results from the trial are expected at an upcoming medical meeting.

Finally, the phase III CASSIOPEIA trial examined bortezomib, thalidomide (Thalomid), and dexamethasone (VTD) with (n = 543) or without (n = 542) daratumumab before and after ASCT in patients with newly diagnosed disease.8 At day 100 after transplantation, 28.9% of patients who received daratumumab plus VTd in the intent-to-treat population achieved a stringent complete response (OR, 1.60; 95% CI, 1.21-2.12; P = .001).

In response to the CASSIOPEIA data, the FDA approved daratumumab for a supplemental indication in combination with VTD for patients who are newly diagnosed and eligible for ASCT.9 “Monoclonal-based quadruplets appear to be safe in induction and posttransplant consolidation,” Usmani concluded. “We are getting deeper responses, adequate stem cell mobilization, as well as an improvement in PFS, but we need long-term follow-up.”

**REFERENCES**

1. Usmani S. Induction and maintenance strategies for transplant eligible NDMM. Slides presented at: Charlotte Plasma Cell Disorders Congress; August 9-11, 2019; Charlotte, NC.
TARGET PD-L1 BLOCKADE

**Indication**

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

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

---

**Efficacy**

- 17% ORR among all patients (2.7% complete response, 14.3% partial response; n=182)\(^1\)
- 26% ORR among PD-L1 high expressers (n=95)\(^1\)
- 4% ORR among PD-L1 low/no expressers (n=73)\(^1\)

- 24% ORR demonstrated among patients who received only prior neoadjuvant or adjuvant therapy\(^1\)

- Median time to response was 6 weeks\(^2\)
  - Based on a secondary endpoint in a single-arm trial
- Median duration of response not yet reached\(^1\)

**Safety**

- Serious potentially fatal risks were seen with IMFINZI; serious adverse reactions occurred in 46% of patients\(^1\)

- The most common Grade 3 or 4 adverse reactions were:
  - Fatigue (6%)
  - Urinary tract infection (4%)
  - Musculoskeletal pain (4%)
  - Abdominal pain (3%)

- The most common adverse reactions were:
  - Fatigue (39%)
  - Musculoskeletal pain (24%)
  - Constipation (21%)
  - Decreased appetite (19%)
  - Nausea (16%)

- Few discontinuations due to adverse events (3.3%)\(^1\)

ORR = overall response rate.

ORR determined by blinded independent central review (BICR) of target lesion diameter according to RECIST v1.1 criteria.

---

**Important Safety Information**

There are no contraindications for IMFINZI® (durvalumab).

IMFINZI can cause serious, potentially fatal adverse reactions including immune-mediated pneumonitis, hepatitis, colitis or diarrhea, endocrinopathies, nephritis, rash or dermatitis, other immune-mediated adverse reactions, infection, and infusion-related reactions. Please refer to the full Prescribing Information for important dosage modification and management information specific to adverse reactions.

Please see Important Safety Information on next page.
TARGET PD-L1 BLOCKADE

Indication
IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
• have disease progression during or following platinum-containing chemotherapy
• have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Choose IMFINZI following platinum-based therapy for your patients with locally advanced or metastatic urothelial carcinoma. Visit IMFINZI.com/hcp

Enable the immune system.
RECOGNIZE. RESPOND.

Efficacy
• 17% ORR among all patients (2.7% complete response, 14.3% partial response; n=182)\textsuperscript{1}
  – 26% ORR among PD-L1 high expressers (n=95)\textsuperscript{1}
  – 4% ORR among PD-L1 low/no expressers (n=73)\textsuperscript{1}
• 24% ORR demonstrated among patients who received only prior neoadjuvant or adjuvant therapy\textsuperscript{1}
• Median time to response was 6 weeks\textsuperscript{2}
  – Based on a secondary endpoint in a single-arm trial
• Median duration of response not yet reached\textsuperscript{1}

ORR=overall response rate.
ORR determined by blinded independent central review (BICR) of target lesion diameter according to RECIST v1.1 criteria.

Safety
• Serious potentially fatal risks were seen with IMFINZI; serious adverse reactions occurred in 46% of patients\textsuperscript{1}
• The most common Grade 3 or 4 adverse reactions were fatigue (6%), urinary tract infection (4%), musculoskeletal pain (4%), and abdominal pain (3%)\textsuperscript{1}
• The most common adverse reactions were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), and nausea (16%)\textsuperscript{1}
• Few discontinuations due to adverse events (3.3%)\textsuperscript{1}

Important Safety Information
There are no contraindications for IMFINZI\textsuperscript{a} (durvalumab).
IMFINZI can cause serious, potentially fatal adverse reactions including immune-mediated pneumonitis, hepatitis, colitis or diarrhea, endocrinopathies, nephritis, rash or dermatitis, other immune-mediated adverse reactions, infection, and infusion-related reactions. Please refer to the full Prescribing Information for important dosage modification and management information specific to adverse reactions.

Please see Important Safety Information on next page.
Important Safety Information (continued)

Immune-Mediated Pneumonitis
IMFINZI can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of pneumonitis and evaluate with radiographic imaging when suspected. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold IMFINZI for Grade 2 pneumonitis; permanently discontinue for Grade 3 or 4 pneumonitis.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, pneumonitis occurred in 5% of patients, including Grade 3 (0.8%), Grade 4 (<0.1%), and Grade 5 (0.3%) pneumonitis. Pneumonitis led to discontinuation of IMFINZI in 1.5% of the 1889 patients. The incidence of pneumonitis (including radiation pneumonitis) was higher in patients in the PACIFIC study who completed treatment with definitive chemotherapy within 42 days prior to initiation of IMFINZI (34%) compared to patients in other clinical studies (2.3%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI.

Immune-Mediated Hepatitis
IMFINZI can cause immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatitis during and after discontinuation of IMFINZI, including clinical chemistry monitoring. Administer corticosteroids for Grade 2 or higher elevations of ALT, AST, and/or total bilirubin. Withhold IMFINZI for ALT or AST greater than 3 but less than or equal to 8 times the ULN or total bilirubin greater than 1.5 but less than or equal to 5 times the ULN; permanently discontinue IMFINZI for ALT or AST greater than 8 times the ULN or total bilirubin greater than 5 times the ULN or concurrent ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN with no other cause.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, hepatitis occurred in 12% of patients, including Grade 3 (4.4%), Grade 4 (0.4%), and Grade 5 (0.2%) hepatitis. Hepatitis led to discontinuation of IMFINZI in 0.7% of the 1889 patients.

Immune-Mediated Colitis
IMFINZI can cause immune-mediated colitis, defined as requiring use of corticosteroids. Administer corticosteroids for Grade 2 or greater colitis or diarrhea. Withhold IMFINZI for Grade 2 colitis or diarrhea; permanently discontinue for Grade 3 or 4 colitis or diarrhea.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, colitis or diarrhea occurred in 18% of patients, including Grade 3 (1.0%) and Grade 4 (0.1%) colitis. Diarrhea or colitis led to discontinuation of IMFINZI in 0.4% of the 1889 patients.

Immune-Mediated Endocrinopathies
IMFINZI can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, and hypophysitis/hypopituitarism. Monitor patients for clinical signs and symptoms of endocrinopathies.

- **Thyroid disorders**—Monitor thyroid function prior to and periodically during treatment. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Withhold IMFINZI for Grades 2–4 hyperthyroidism, until clinically stable. Continue IMFINZI for hypothyroidism.

  In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, hypothyroidism occurred in 11% of patients, while hyperthyroidism occurred in 7% of patients. Thyroiditis occurred in 0.9% of patients, including Grade 3 (<0.1%). Hypothyroidism was preceded by thyroiditis or hyperthyroidism in 25% of patients.

- **Adrenal insufficiency**—Administer corticosteroids as clinically indicated and withhold IMFINZI until clinically stable for Grade 2 or higher adrenal insufficiency. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, adrenal insufficiency occurred in 0.7% of patients, including Grade 3 (<0.1%) adrenal insufficiency.

- **Type 1 diabetes mellitus**—Initiate treatment with insulin as clinically indicated. Withhold IMFINZI for Grades 2–4 type 1 diabetes mellitus, until clinically stable. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, type 1 diabetes mellitus occurred in <0.1% of patients.

- **Hypophysitis**—Administer corticosteroids and hormone replacement as clinically indicated and withhold IMFINZI until clinically stable for Grade 2 or higher hypophysitis. Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in <0.1% of 1889 patients with various cancers who received IMFINZI.

Immune-Mediated Nephritis
IMFINZI can cause immune-mediated nephritis, defined as evidence of renal dysfunction requiring use of corticosteroids. Fatal cases have occurred. Monitor patients for abnormal renal function tests prior to and periodically during treatment with IMFINZI. Administer corticosteroids as clinically indicated. Withhold IMFINZI for creatinine greater than 1.5 to 3 times the ULN; permanently discontinue IMFINZI and administer corticosteroids in patients with creatinine greater than 3 times the ULN.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, nephritis (reported as any of the following: increased creatinine or urea, acute kidney injury, renal failure, decreased glomerular filtration rate, tubulointerstitial nephritis, decreased creatinine clearance, glomerulonephritis, and nephritis) occurred in 6.3% of the patients including Grade 3 (1.1%), Grade 4 (0.2%), and Grade 5 (0.1%) nephritis. IMFINZI was discontinued in 0.3% of the 1889 patients.

Immune-Mediated Dermatologic Reactions
IMFINZI can cause immune-mediated rash. Bullous dermatitis and Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) have occurred with other products in this class. Administer corticosteroids for Grade 2 rash or dermatitis lasting for more than 1 week or for Grade 3 or 4 rash or dermatitis. Withhold IMFINZI for Grade 2 rash or dermatitis lasting longer than 1 week or Grade 3 rash or dermatitis; permanently discontinue IMFINZI in patients with Grade 4 rash or dermatitis.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, 26% of patients developed rash or dermatitis and 0.4% of the patients developed vitiligo. Rash or dermatitis led to discontinuation of IMFINZI in 0.1% of the 1889 patients.
Other Immune-Mediated Adverse Reactions

IMFINZI can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with IMFINZI, immune-mediated adverse reactions can also manifest after discontinuation of IMFINZI. For suspected immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. Withhold IMFINZI for Grade 3 immune-mediated adverse reactions, unless clinical judgment indicates discontinuation; permanently discontinue IMFINZI for Grade 4 adverse reactions.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1889 patients who received IMFINZI: aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis. Additional clinically significant immune-mediated adverse reactions have been seen with other products in this class (see Warnings and Precautions Section 5.7 of IMFINZI full Prescribing Information).

Infection

IMFINZI can cause serious infections, including fatal cases. Monitor patients for signs and symptoms of infection and treat as clinically indicated. Withhold IMFINZI for Grade 3 or 4 infection, until clinically stable.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, infections occurred in 43% of patients, including Grade 3 (8%), Grade 4 (1.9%), and Grade 5 (1.0%). The overall incidence of infections in IMFINZI-treated patients in the PACIFIC study (56%) was higher compared to patients in other clinical studies (38%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI. In patients with UC in Study 1108 (n=182), the most common Grade 3 or higher infection was urinary tract infections, which occurred in 4% of patients.

Infusion-Related Reactions

IMFINZI can cause severe or life-threatening infusion-related reactions. Monitor patients for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion for Grades 1–2 infusion-related reactions; permanently discontinue for Grades 3–4 infusion-related reactions.

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI, infusion-related reactions occurred in 2.2% of patients, including Grade 3 (0.3%).

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. There are no data on the use of IMFINZI in pregnant women. Advise pregnant women of the potential risk to a fetus and advise women of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI.

Lactation

There is no information regarding the presence of IMFINZI in human milk; however, because of the potential for adverse reactions in breastfed infants from IMFINZI, advise women not to breastfeed during treatment and for at least 3 months after the last dose.

Most Common Adverse Reactions

- In patients with UC in Study 1108 (n=182), the most common adverse reactions (≥15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%), and urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

- In patients with UC in Study 1108, discontinuation due to adverse reactions occurred in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (≥2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, and pyrexia/tumor associated fever (2.7% each).

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

Please see Brief Summary of complete Prescribing Information on adjacent page.

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.

IMFINZI® (durvalumab) injection, for intravenous use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

Urothelial Carcinoma

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjunct treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [see Clinical Studies (14.1) in the full Prescribing Information].

Dosage and Administration

Recommended Dosage for Urothelial Carcinoma

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity.

Dosage Modifications for Adverse Reactions

No dose reductions are recommended. Withhold or discontinue IMFINZI to manage adverse reactions as described in Table 1.

Table 1. Recommended Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Grade 2</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Grade 3 or 4</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Colitis or diarrhea</td>
<td>Grade 2</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanent discontinuation</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
</tr>
<tr>
<td>Adrenal insufficiency/Hypophysitis</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
</tr>
<tr>
<td>Nephritis</td>
<td>Grade 2 for longer than 1 week or Grade 3</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>Grade 1 or 2</td>
<td>Interrupt or slow the rate of infusion</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Other immune-mediated adverse reactions</td>
<td>Grade 3</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)</td>
<td>Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last IMFINZI dose</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

Preparation and Administration

Preparation

- Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or contains visible particles.
- Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL.
- Discard partially used or empty vials of IMFINZI.

Storage of Infusion Solution

- IMFINZI does not contain a preservative.
- Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the total time from vial puncture to the start of the administration should not exceed:
  - 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F)
  - 4 hours at room temperature up to 25°C (77°F)

- Do not freeze.
- Do not shake.

Administration

- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other drugs through the same infusion line.

Contraindications

None.

Warnings and Precautions

Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent for more severe (Grade 3-4) pneumonitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], pneumonitis occurred in 5% of patients, including Grade 3 (0.8%), Grade 4 (0.1%) and Grade 5 (0.3%) immune-mediated pneumonitis. The median time to onset was 1.8 months (range: 1 day to 13.9 months) and the median time to resolution was 4.9 months (range: 0 days to 137.3 months).

Pneumonitis led to discontinuation of IMFINZI in 1.5% of the 1889 patients. Pneumonitis resolved in 54% of patients. Systemic corticosteroids were required in 3.5% of the 1889 patients, with 2.5% requiring high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) and 0.1% requiring infliximab.

Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of IMFINZI, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent, followed by taper for Grade 2 or higher elevations of ALT, AST, and/or total bilirubin. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], hepatitis occurred in 12% of patients, including Grade 3 (4.4%), Grade 4 (0.4%) and Grade 5 (0.2%) immune-mediated hepatitis. The median time to onset was 1.2 months (range: 1 day to 13.6 months). Hepatitis led to discontinuation of IMFINZI in 0.7% of the 1889 patients. Hepatitis resolved in 49% of patients. Systemic corticosteroids were required in 2.7% of patients, with 1.7% requiring high-dose corticosteroids and 0.1% requiring mycophenolate.

Immune-Mediated Colitis

IMFINZI can cause immune-mediated colitis, defined as requiring use of corticosteroids.

Monitor patients for signs and symptoms of diarrhea or colitis. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or more severe (Grade 3-4) colitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], diarrhea or colitis occurred in 16% of patients, including Grade 3 (1%) and Grade 4 (0.1%) immune-mediated colitis. The median time to onset was 1.4 months (range: 1 day to 14 months). Diarrhea or colitis led to discontinuation of IMFINZI in 0.4% of the 1889 patients. Diarrhea or colitis resolved in 78% of the patients. Systemic corticosteroids were required in 1.9% of patients, with 1% requiring high-dose corticosteroids and 0.1% requiring other immunosuppressants (e.g., infliximab, mycophenolate).
Immune-Mediated Endocrinopathies IMFINZI can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, diabetes mellitus and hyperthyroidism. Thyroid Disorders: Monitor thyroid function prior to and periodically during treatment with IMFINZI. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continual IMFINZI for hyperthyroidism and interrupt for hypothyroidism based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. In clinical studies enrolling 1889 patients who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], hyperthyroidism occurred in 11% of patients and hyperthyroidism occurred in 7% of patients. Thyroiditis occurred in 0.9% of patients, including Grade 3 (0.1%) thyroiditis. Hypothyroidism was preceded by thyrotoxicosis or hyperthyroidism in 25% of patients. Adrenal Insufficiency: Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1 to 2 mg per kg per day or equivalent, followed by corticosteroid taper and hormone replacement as clinically indicated. Interrupt IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. In clinical studies enrolling 1889 patients who received IMFINZI, adrenal insufficiency occurred in 0.7% of patients, including Grade 3 (0.1%) adrenal insufficiency. Systemic corticosteroids were required in 0.4% of patients. including 0.1% of patients who required high-dose corticosteroids. Type 1 Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. In clinical studies enrolling 1889 patients who received IMFINZI, type 1 diabetes mellitus occurred in < 0.1% of patients. The median time to onset was 1.4 months. Hypophysitis: For Grade 2 or higher hypophysitis, initiate prednisone 1 to 2 mg per kg per day or equivalent, followed by corticosteroid taper and hormone replacement therapy as clinically indicated. Interrupt IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. Hypophysitis leading to adrenal insufficiency and diabetes insipidus occurred in < 0.1% of 1889 patients who received IMFINZI in clinical studies. Immune-Mediated Nephritis IMFINZI can cause immune-mediated nephritis defined as evidence of renal dysfunction, require- ment for corticosteroids. Fatal cases have occurred. Monitor patients for abnormal renal function tests prior to and periodically during treatment with IMFINZI. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or severe (Grade 3-4) nephritis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], nephritis (reported as any of the following increased creatinine or urine, acute kidney injury, renal failure, decreased glomerular filtration rate, tubulointerstitial nephritis, decreased creatinine clearance, glomerulonephritis, and nephritis) occurred in 6.3% of patients including Grade 1 (1.1%), Grade 4 (0.2%) and Grade 5 (0.1%) immune-mediated nephritis. The median time to onset was 2 months (range: 1 day to 14.2 months). IMFINZI was discontinued in 0.3% of the 1889 patients. Nephritis resolved in 50% of patients. Systemic cortico- steroids were required in 0.6% of patients, with 0.4% receiving high-dose corticosteroids. Immune-Mediated Dermatologic Reactions IMFINZI can cause immune-mediated rash: bullous dermatitis, Stevens Johnson Syndrome (SJS)/ toxic epidermal necrolysis (TEN) have occurred with other products in this class [see Warnings and Precautions (5.4)]. Monitor for signs and symptoms of rash. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or severe (Grade 3-4) rash, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], 26% of patients developed rash or dermatitis and 4.4% of the patients developed vellus. Rash or dermatitis led to discontinuation of IMFINZI in 0 of 1,889 patients. Rash resolved in 52% of patients. Systemic corticosteroids were required in 2.0% of patients, including high-dose corticosteroids in 1% of patients. Other Immune-Mediated Adverse Reactions IMFINZI can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with IMFINZI, immune-mediated adverse reactions can also manifest after discontinuation of IMFINZI. For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 4 mg per kg per day or equivalent, followed by taper. Interrupt or permanently discontinue IMFINZI, based on the severity of the reaction [see Dosage and Administration (2.3) in the full Prescribing Information]. If ulcers occur in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed with other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss. The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1889 patients who received IMFINZI: acyclic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocardiitis, myositis, and ocular inflammatory toxicity, including optic neuritis [see Adverse Reactions (6.1) in the full Prescribing Information]. The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, systemic inflammatory response syndrome, thrombocytopenia, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, iritis, encephalitis, facial and abducens nerve paralysis, demyelination, polyneuropathy, autoimmune neuropathy, Guillain-Barre syndrome and Vogt-Koyanagi-Harada syndrome. Infection IMFINZI can cause serious infections, including fatal cases. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold IMFINZI and resume once clinically stable [see Dosage and Administration (2.3) in the full Prescribing Information]. In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1) in the full Prescribing Information], infections occurred in 43% of patients, including Grade 3 (6%), Grade 4 (1.9%), and Grade 5 (1.0%). In the uterine cervical carcinoma cohort in Study 1188 the most common Grade 3 or higher infection was urinary tract infections, which occurred in 4% of patients. Infusion-Related Reactions IMFINZI can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions, interrupt, slow the rate of, or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3) in the full Prescribing Information]. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses. In clinical studies enrolling 1889 patients with various cancers [see Adverse Reactions (6.1) in the full Prescribing Information], infusion-related reactions occurred in 2.2% of patients, including Grade 3 (0.3%). Because Fetal Toxicity Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased premature delivery, fetal loss and premature neonatal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI [see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]. ADVERSE REACTIONS The following adverse reactions are discussed in greater detail in other sections of the labeling. • Immune-Mediated Pneumonitis [see Warnings and Precautions (5.1) in the full Prescribing Information]. • Immune-Mediated Hepatitis [see Warnings and Precautions (5.2) in the full Prescribing Information]. • Immune-Mediated Colitis [see Warnings and Precautions (5.3) in the full Prescribing Information]. • Immune-Mediated Endocrinopathies [see Warnings and Precautions (5.4) in the full Prescribing Information]. • Immune-Mediated Nephritis [see Warnings and Precautions (5.5) in the full Prescribing Information]. • Immune-Mediated Dermatologic Reactions [see Warnings and Precautions (5.6) in the full Prescribing Information]. • Other Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.7) in the full Prescribing Information]. • Infusion [see Warnings and Precautions (5.8) in the full Prescribing Information]. • Infusion-Related Reactions [see Warnings and Precautions (5.9) in the full Prescribing Information]. Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflect exposure to IMFINZI in 1889 patients from the PACIFIC study (a randomized, placebo-controlled study that enrolled 475 patients with Stage III NSCLC), Study 1108 (an open-label, single-arm, multicohort study that enrolled 191 patients with uterine cervical carcinoma and 779 patients with various other solid tumors), and in an additional open-label, single-arm trial that enrolled 444 patients with metastatic lung cancer, an indication for which durvalumab is not approved. Across all studies, IMFINZI was administered at a dose of 10 mg/kg intravenously every 2 weeks [see Clinical Studies (14.1) in the full Prescribing Information]. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses. In clinical studies enrolling 1889 patients with various cancers [see Adverse Reactions (6.1) in the full Prescribing Information], infusion-related reactions occurred in 2.2% of patients, including Grade 3 (0.3%).
Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 1% of Patients in Study 1108 Urothelial Carcinoma Cohort

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3 - 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>12</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>1</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1</td>
</tr>
<tr>
<td>Hyperalbuminemia</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Adverse Reactions in ≥ 10% of Patients in Study 1108 Urothelial Carcinoma Cohort

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMFINZI N=182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>21 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 3</td>
</tr>
<tr>
<td>Diarrhea/Colic</td>
<td>13 1</td>
</tr>
<tr>
<td>General Disorders and Administration</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 6</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15 2</td>
</tr>
<tr>
<td>Pyrexia/Tumor associated fever</td>
<td>14 1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15 4</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>19 1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>21 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 3</td>
</tr>
<tr>
<td>Diarrhea/Colic</td>
<td>13 1</td>
</tr>
<tr>
<td>General Disorders and Administration</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 6</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15 2</td>
</tr>
<tr>
<td>Pyrexia/Tumor associated fever</td>
<td>14 1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15 4</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>19 1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>21 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 3</td>
</tr>
<tr>
<td>Diarrhea/Colic</td>
<td>13 1</td>
</tr>
<tr>
<td>General Disorders and Administration</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 6</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15 2</td>
</tr>
<tr>
<td>Pyrexia/Tumor associated fever</td>
<td>14 1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15 4</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) in the full Prescribing Information). There are no data on the use of IMFINZI in pregnant women. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery resulted in an increase in premature delivery, fetal loss and premature neonatal death (see Data). Human immunoglobulin G1 (IgG1) is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing fetus. Apprise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy. Premature delivery, fetal loss and stillbirth and increases in neonatal deaths. Durvalumab was detected in rat fetal serum on postnatum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Lactation

Risk Summary

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (see Data). Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data

In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature neonatal death.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1) in the full Prescribing Information). Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months following the last dose of IMFINZI.

Pediatric Use

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

Geriatric Use

Of the 182 patients treated with IMFINZI in patients with urothelial carcinoma, 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15% (17/112) and was 12% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older.

OVERDOSAGE

There is no information on overdose with IMFINZI.

PATIENT COUNSELING INFORMATION

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

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1) in the full Prescribing Information].
- Hepatitis: Advise patients to contact their healthcare provider immediately if jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see Warnings and Precautions (5.2) in the full Prescribing Information].
- Collitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain [see Warnings and Precautions (5.3) in the full Prescribing Information].
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism, hypothyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypophysitis [see Warnings and Precautions (5.4) in the full Prescribing Information].
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see Warnings and Precautions (5.5) in the full Prescribing Information].
- Dermal toxicities: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermal reactions [see Warnings and Precautions (5.6) in the full Prescribing Information].
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of septic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis [see Warnings and Precautions (5.7) in the full Prescribing Information].
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.8) in the full Prescribing Information].
- Embryo-Fetal Toxicity: Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1) in the full Prescribing Information].
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.8) in the full Prescribing Information].
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of septic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis [see Warnings and Precautions (5.7) in the full Prescribing Information].
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.8) in the full Prescribing Information].
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of septic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis [see Warnings and Precautions (5.7) in the full Prescribing Information].
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.8) in the full Prescribing Information].
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of septic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis [see Warnings and Precautions (5.7) in the full Prescribing Information].
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.8) in the full Prescribing Information].
Surgery Retains Important Role in Evolving RCC Paradigm

by JESSICA HERGERT

THE RENAL CELL CARCINOMA (RCC) landscape has witnessed a shift in the role of surgery with the introduction of immunotherapy, combination regimens, and novel agents; nonetheless, it is still an important modality to consider, explained Robert G. Uzzo, MD, MBA, FACS.

“Twenty years ago when the Von Hippel-Lindau [tumor suppressor] gene was identified, nobody would have realized the monumental shift in patient care [it would cause], which benefits not only longevity of life but quality of life,” explained Uzzo. “Before that, [patients’ options were] interferon and/or clinical trials. Now we have so many therapies for patients with advanced kidney cancer.”

Even with the addition of these systemic regimens, surgery continues to have an integral role, and a growing one for patients with metastatic disease, he added.

In an interview with OncologyLive® during the 2019 Kidney Cancer Research Summit, Uzzo discussed the evolving role of surgery in RCC. He is professor of surgery in the Temple University Health System and chair of the Department of Surgical Oncology at Fox Chase Cancer Center, both in Philadelphia.

Q: What do you see coming down the pipeline in RCC?

I’m a surgeon, so I spend much of my time thinking about the biology of the tumor and whether or not surgery can intervene for a therapeutic benefit. In the past, when we did not have a lot of systemic therapy, surgery usually was the answer. It may be uncommon for a surgeon to talk about a diminishing role in the management of kidney cancer; however, [surgery has] a growing role in patients with metastatic disease.

A lot of new data, mostly from the CARMENA [NCT00930033] and SURTIME [NCT01099423] trials, have emerged regarding whether surgery should be upfront for patients with metastatic disease. There is recognition now that patients are served by having upfront systemic therapy. These patients get upfront systemic therapy and then become good responders [demonstrating] prolonged, durable complete responses or partial responses. The question then becomes, “How do you consolidate the results of the systemic therapies with surgery?”

We are talking about the idea of lifelong therapies for people who are not cured. If we could get them to a point where they have got a significant partial response from dual therapy or from combinations, and could then take them to the operating room and excise them, can we now give them a period of time where they are off of therapy?

Yes, we could discuss the mechanistic aspects of new therapies that are coming down [the pipeline], the HIF [hypoxia inducible factor] inhibitors and other combinations and sequential therapies, but surgery is evolving. The role of surgery in patients with metastatic disease may look a lot different 3 to 5 years from now.

Q: What factors determine whether a patient should receive neoadjuvant therapy, adjuvant therapy, or upfront surgery?

The question about adjuvant therapy and neoadjuvant therapy is something that is still not settled. A lot of clinical trials and level I evidence suggest that we haven’t hit on the right combination, certainly for adjuvant therapy.

Right now, in the immunotherapy era, a lot of studies are asking questions such as, “Do you need to use immunotherapy before surgery or after?” We haven’t gotten to the point where we have multiple agents being used in the adjuvant setting, although trials [are ongoing].

The jury is out, and it is a hard conversation to have with a person. From a surgical perspective, you bring a patient to the operating room, you remove their stage III kidney cancer—essentially rendering them surgically R0, or no evidence of disease. However, the risk of recurrence is high. You want to give the patient good news, but you have to temper that enthusiasm with the risk of recurrence.

In terms of the neoadjuvant setting, most people think, based on CARMENA and SURTIME, that patients with metastatic, high-risk disease ought to have systemic therapy first. The real question surrounds the favorable-risk, young patients with lung-only metastatic disease. Most likely, a portion of patients would benefit from surgery upfront followed by a potential period of time off of systemic therapy. The goal isn’t just longevity but quality of life, which is impacted both by surgery and systemic therapies.

Q: Does a rationale exist for trying the combinations that are approved in the metastatic setting either before or after surgery?

Certainly, the idea is that if it works for stage IV disease, it probably works in the adjuvant setting—or it should work. The question is, “How robust of a signal can we get?” Those data take a long time to mature. I suspect that the earliest read-out that we will see for immunotherapy in the adjuvant setting is going to be another 2 to 3 years.

Q: What other research are you conducting that you’d like to highlight?

One of the sessions I co-chaired at the [2019 Kidney Cancer Research Summit] was on novel delivery mechanisms. We discussed whether there are ways to focally deliver novel systemic therapies, such as immunotherapies or nanoparticles directly injected into the tumor. Those delivery mechanisms and the engineering of them is the next frontier.

Q: What should clinicians be cognizant of in the RCC field?

The most important thing that clinicians should know about—and we do intuitively know about—is that the science drives the cure. This was a discussion about how the science today may look for the cure not just 10 years from now, but perhaps with a compressed time frame. We live in a time in which “big data” are allowing us to deliver [cures] much quicker. Clinical trials take a long time, but [the time from] discovery to therapeutic benefit is compressed. That’s an important point.
Can New Oncology Payment Programs Help Stabilize Medicare?

By MARCUS NEUBAUER, MD, AND JAD HAYES, MS

DUE TO THE HIGH cost of cancer care, the oncology landscape is under intense scrutiny from the Centers for Medicare & Medicaid Services (CMS) and commercial payers. Cost trends in oncology demonstrate that what Medicare pays for cancer care is unsustainable and changes must occur or the program will soon be insolvent. Medicare’s hospital insurance trust fund is projected to be depleted by 2026. If this happens, more financial burden will shift to patients or care for Medicare beneficiaries may not be available.

Studies have raised doubts about the value Medicare and other payers are getting for the care they pay for, including in oncology. This has intensified the demand for new value-based care models such as the Merit-based Incentive Payment System (MIPS) and the Oncology Care Model (OCM). The OCM is an alternative payment model from the Center for Medicare & Medicaid Innovation (CMMI), an organization under CMS that develops new healthcare payment and service delivery models. The voluntary, 5-year pilot program will end in June 2021 and could be replaced by another complex value-based model. Oncology practices not participating in the OCM are in MIPS, as are most providers who care for patients with Medicare coverage.

The overarching goals of both programs are to better manage costs, deliver higher-quality care, and improve the patient experience. But are these programs actually achieving cost reductions, especially in oncology, that can help stabilize the costs to Medicare? Are they generating the desired improvements in quality of care and patient experience? Now that we are several years into both programs, these questions are worth a closer look.

IS IT POSSIBLE TO REDUCE COSTS AND PROVIDE BETTER CARE?

Both MIPS and the OCM are part of CMS’ strategy to transition to paying for value rather than volume. Both programs have been thoughtfully designed to try and maintain or improve quality while maintaining or decreasing costs. However, they have several differences. For example, the OCM provides incentive payments for practice transformation to meet CMS’ Triple Aim of better care for individuals, better health for populations, and lower costs per capita. MIPS does not provide funding for change. The OCM is a steeper ramp to value-based care with more financial investment required. MIPS is a slower route to that objective.

THE ONCOLOGY CARE MODEL

Based on our experience with practices in The US Oncology Network (The Network) that are participating in the OCM, the program appears to be meeting its major goals of improving care while reducing costs. However, performing well in the OCM is extremely challenging and does not happen overnight. It requires a significant amount of practice transformation. The program was designed to support a better way to deliver care by funding practice transformation. Practices receive a Monthly Enhanced Oncology Services (MEOS) fee of $160 for each patient enrolled in the OCM. MEOS payments compensate for management and coordination of care. This additional funding enables practices to add nurse navigators, social workers, and other highly trained staff who enhance the patient experience while facilitating care that is more cost-effective.

Across participating practices in The Network, care has improved with the OCM, largely because the additional staff provide more touch points for patients. For instance, many practices utilize team huddles to identify at-risk patients. This enables more preemptive care to better manage adverse events, keeping patients healthier and out of the hospital. With additional staff, practices are also more proactive in coordinating care and facilitating advance care planning discussions that improve patients’ quality of life during therapy and when therapy is no longer effective. Overall, the structure and requirements of the program have facilitated better care, and patient feedback has verified a higher level of satisfaction.

Realizing savings with the OCM is also possible. The program uses a very sophisticated mathematical model to determine what a practice should spend versus what is actually spent. The goal is for practices to generate a cost curve lower than for providers not in the program. Many of The Network practices participating in the OCM have been very successful in adapting their clinics to the model, achieving substantial savings for Medicare.

Preemptive care, a major component of the OCM, contributes greatly to cost savings. For instance, hospitalizations are a major expense in cancer care. A recent study found the average cost of nausea- and vomiting-related hospitalizations among patients with cancer exceeds $15,000 per event. Effectively managing pain and other symptoms reduces expensive hospital admissions and emergency department visits. Advance care
planning not only provides high-quality care for patients, but also saves money by decreasing ineffective and often undesired end-of-life care. Whether cost savings such as these are significant enough to help stabilize Medicare remains to be seen, but the OCM is, at least, a good start.

There are, however, concerns about the program. The biggest cost in the OCM is drugs. The costs of cancer drugs continue to increase and are out of providers’ control. Mechanisms are built into the OCM to prevent cost outliers from disrupting the model, but it is a difficult balance to achieve. The success of the model depends on its being able to compensate physicians adequately for episodes of care. However, a new drug may come into play that offers improved outcomes and it alone may cost more than the entire episode of care is projected to cost. When this happens, the practice may be penalized even though the choice of therapy was backed by solid evidence. There is a long list of cancer drugs in the pipeline, so this problem is not going away anytime soon.

There are also some flaws in the model that are causing difficulties for some practices. Despite doing a good job of implementing the changes needed to improve delivery of cost-effective care, some practices are not meeting financial targets in the program, and it is difficult to discern the root causes given the complex structure of the model. Target prices are difficult to achieve without more clarity on cost drivers and how benchmark care prices are determined. The OCM still needs some fine-tuning to better understand situations like these.

All things considered, it appears the OCM can provide better patient care and reduce overall costs to Medicare. Performance by a large number of practices across The Network has demonstrated these goals are not mutually exclusive. The Network has 15 practices participating in the OCM, and 13 have beat benchmark pricing in the most recent performance period. On the quality-of-care side, all 15 practices have qualified to share robustly in the amount of savings achieved.

THE MERIT-BASED INCENTIVE PAYMENT SYSTEM

The 2015 Medicare Access and CHIP Reauthorization Act combined several incentive programs into one: MIPS. MIPS is a very ambitious program and is much larger than the OCM because most providers, not just oncologists, who care for patients with Medicare coverage are required to participate. Much like the OCM, the idea behind MIPS is to transition away from volume of care to a focus on quality, value, and accountability.

Unfortunately, the guidance and feedback practices have received so far have been very slim. Many providers are unclear about what the program is trying to do and what they must do to succeed. Performance on various quality metrics is compared with the metrics from other practices, specialty by specialty. Practices that do well receive a positive adjustment on services billed 2 years after the MIPS calendar year. The 11 practices in The Network participating in MIPS have qualified to receive positive payment adjustments in Part B payments based on improvements in cost and value. Reporting requirements, however, are quite extensive, and providers struggle to meet them. At least for now, practices receive little in return for the amount of effort they expend.

CONTINUED ON PAGE 77
Radiation Oncology Model Will Not Satisfy Need for Payment Reform

by PAUL HARARI, MD, FASTRO

IN JULY 2019, CENTERS FOR MEDICARE & MEDICAID (CMS) proposed the Radiation Oncology (RO) Model, an important step forward in allowing the nation’s 4500 radiation oncologists to join in the transition to value-based healthcare, as envisioned by the 2015 Medicare Access and CHIP Reauthorization Act (MACRA).

The American Society for Radiation Oncology (ASTRO)—the leading medical society for members of the RO care team—submitted comments to CMS in September 2019 to express its appreciation for the agency’s decision to move forward with an alternative payment model (APM) for the specialty. However, ASTRO leaders have shared multiple concerns about the proposal, such as the model’s mandatory nature and its excessive payment cuts to practices. Below is a review of the strengths and shortcomings of the proposed RO Model, as well as suggested policy solutions to ensure the model can achieve its intended goals of improving patient outcomes while generating savings for Medicare.

Compared with the current fee-for-service structure that incentivizes volume over value in Medicare payment, an APM for RO could realign incentives to encourage the use of guideline-concordant and efficient patient care. A successful RO Model also could create stable and predictable payment rates that avoid jeopardizing patient access to life-saving treatments and support medical innovation while reducing administrative burden.

Our organization appreciates that CMS recognizes the effort that radiation oncologists have put into the development of an APM for their specialty, as evidenced by the fact that several elements of the proposed CMS RO Model align with the Radiation Oncology Alternative Payment Model concept paper that ASTRO submitted to CMS in April 2017. The positive aspects of the CMS model include the prospective payment; the episode trigger mechanism, timeline and clean period; establishment of distinct professional component and technical component payments; the inclusion of all modalities of treatment; and key quality measure elements.

We are concerned, however, that the proposed CMS RO Model falls short of meeting 3 key goals that ASTRO identified in comments submitted to CMS as necessary for successful, longstanding payment reform. From our perspective, an APM for RO should:

1. Reward radiation oncologists for participation and performance in quality initiatives that improve the value of healthcare for patients;
2. Ensure fair, predictable payment for the radiation oncologist in both hospital and freestanding cancer clinics to protect patients’ access to care in all settings; and
3. Incentivize the appropriate use of cancer treatments that result in the highest quality of care and the best patient outcomes.

An ASTRO analysis estimates that the RO Model would cut payments to participants by approximately $320 million during the 5-year period—an excessive amount that would undermine this unique opportunity. Cuts of this magnitude could strain RO practices that have little choice but to take part in the model, which could put access to safe and effective radiation treatments at risk. For the RO Model to be successful, ASTRO recommends specific, significant changes that will incentivize the use of high-quality, efficient radiation therapy treatments that drive value-based reform and generate savings for Medicare. A summary of the key issues and recommended ASTRO policy solutions to address them follow:

- **Mandatory participation** that extends to 40% of RO episodes is excessive for an untested model. **ASTRO recommends** that CMS should begin with voluntary participation before moving to a mandatory model, while allowing opt-outs for low-volume practices and hardship exceptions.
- **National case rates.** Calculations for the national case rates contain flaws that would result in significant and unfair payment penalties. **ASTRO leaders** are concerned that the methodology fails
to appropriately account for a range of complex clinical scenarios and average treatment costs for many clinics. ASTRO recommends that CMS include some costs from the Medicare Physician Fee Schedule, properly attribute palliative care cases, and ensure adequate payments for patients receiving standard-of-care multimodality treatments, such as combination therapy for gynecological cancer.

- **Discount factor and efficiency adjustment.** Proposed adjustments could result in significant funding cuts to all participants and unfairly harm practices that are already efficient. ASTRO recommends that CMS adjust the efficiency factor to avoid penalizing efficient practices and scale back the discount factors, which put patient access at risk by causing significant financial issues for such a capital expenditure-intensive specialty.
- **APM incentive payment.** CMS’ selective waiver of the 5% APM incentive payment on freestanding center technical payments does not align with either the spirit or the letter of MACRA, which calls for giving providers incentives to take on risk by participating in APMs. ASTRO recommends removing this waiver.

- **Innovation.** Advances in RO have increased cure rates and reduced adverse effects from treatment. Yet, the RO Model does not adequately account for future innovation in the delivery of RO. Practices should be able to continue to invest in technology and other changes that provide clinical benefit for patients. ASTRO recommends that CMS pay for new technology at fee-for-service rates and adopt a rate review mechanism for new service lines and upgrades.

- **Burden.** The proposed RO Model would heap additional administrative tasks and costly requirements on already burdened RO practices that are required to participate in the model. ASTRO recommends that CMS delay many of these requirements and rely instead on recommendations from the RO community to ensure that only information that is most meaningful and least burdensome is collected.

ASTRO believes the RO Model, with significant modifications, could represent a meaningful and viable first step toward enabling the field of RO to participate in the evolving world of healthcare payment reform, as initiated by MACRA. The proposed model has serious flaws, but none of these issues are insurmountable. Radiation oncologists are committed to working with CMS to modify the model in such a way that it meets the stated goals.

For a full list of references, see the article at ajmc.com/link/4333.
THESE ARE PATIENTS WITH
METASTATIC GASTRIC,
NON–SMALL CELL LUNG,
OR COLORECTAL CANCER.

PATIENTS WHOSE DISEASE HAS PROGRESSED
ON PRIOR TREATMENT.*

PATIENTS WHO KNOW THEIR SITUATION, BUT ARE
NOT SURRENDERING TO IT.

PATIENTS WHO, IN THE FACE OF ADVERSITY,
REMAIN DETERMINED.

LEARN MORE ABOUT THE APPROPRIATE PATIENTS
FOR CYRAMZA AT CYRAMZAHCP.COM

*Hypothetical patient example.

SELECT IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Please see additional Important Safety Information for CYRAMZA, including Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on adjacent page. Also see the Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
"We have some unfinished business."

**METASTATIC GASTRIC OR GEJ ADENOCARCINOMA**

**INDICATION**
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

"Whatever’s next, I want to be all in."

**METASTATIC NON–SMALL CELL LUNG CANCER**

**INDICATION**
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

"I’m ready to do what it takes."

**METASTATIC COLORECTAL CANCER**

**INDICATION**
CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

---

Hypothetical patient example.

**INDICATION**
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

**METASTATIC GASTRIC OR GEJ ADENOCARCINOMA**

**INDICATION**
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

**METASTATIC NON–SMALL CELL LUNG CANCER**

**INDICATION**
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

**METASTATIC COLORECTAL CANCER**

**INDICATION**
CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
**INDICATIONS**

CYRAMZA® (ramucirumab) injection RB-P HCP BS 27MAR2017

**CYRAMZA® (ramucirumab) injection RB-P HCP BS 27MAR2017**

**CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic gastrectomy or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of clinically relevant bleeding.**

**WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING**

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, and should be monitored in patients with gastrectomy in combination with docetaxel. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

**Warnings and Precautions**

**Hemorrhage**

- In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel in advanced gastric cancer, the incidence of severe bleeding was 4.5% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) or other anticoagulants were excluded from enrolment in studies 1 and 2. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other anticoagulants other than aspirin were excluded from study 3. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI.

**Arterial Thromboembolic Events (ATEs)**

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

**Hypertension**

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) compared to placebo (3%), in patients receiving CYRAMZA plus paclitaxel (15%) compared to placebo plus paclitaxel (5%), and in patients receiving CYRAMZA plus docetaxel (6%) compared to placebo plus docetaxel (2%); and in patients receiving CYRAMZA plus FOLFIRI (11%) compared to placebo plus FOLFIRI (5%). Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions (IRRs)**

- Peri- or intravascular administration of CYRAMZA should be administered at a rate not exceeding 0.5 mg/min for patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of clinically relevant bleeding.

**Gastrointestinal Perforations**

- Four of 570 patients (0.7%) who received CYRAMZA as a single agent in advanced gastric cancer clinical trials experienced gastrointestional perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placeo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**Impaired Wound Healing**

- CYRAMZA has not been evaluated in patients with severe or nonhealing wounds. CYRAMZA has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops worsening of proteinuria during CYRAMZA therapy, permanently discontinue CYRAMZA.

**Clinical Deterioration in Child-Pugh B or C Cirrhosis**

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Discontinue CYRAMZA in patients who develop RPLS. Symptomatic RPLS, as defined with RPLS with clinical manifestations, can experience ongoing neurologic sequelae or death.

**Proteinuria Including Nephrotic Syndrome**

- In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein/creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g per 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to ≤2 g per 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g per 24 hours or in the setting of nephrotic syndrome.

**Thyroid Dysfunction**

- Monitor thyroid function during treatment with CYRAMZA. In study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

**Emboliform Blood Clots**

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angioinversion, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryological development, and postnatal development. Advise pregnant women of the potential risk of use, effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

**Most Common Adverse Reactions—Single Agent**

- The most commonly reported adverse reactions (all grades; grade 3 or 4) occurring in ≥5% of patients receiving CYRAMZA as monotherapy were proteinuria (1.5%) and gastrointestinal perforation (1.7%). In study 2, severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein/creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g per 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to ≤2 g per 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g per 24 hours or in the setting of nephrotic syndrome.

**Most Common Adverse Reactions—Combination With Paclitaxel**

- The most commonly reported adverse reactions (all grades; grade 3 or 4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel were proteinuria (15%) and gastrointestinal perforation (15%). In study 2, severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein/creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g per 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to ≤2 g per 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g per 24 hours or in the setting of nephrotic syndrome.

**Most Common Adverse Reactions—Combination With Docetaxel**

- The most commonly reported adverse reactions (all grades; grade 3 or 4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel were proteinuria (15%) and gastrointestinal perforation (15%). In study 2, severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein/creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g per 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to ≤2 g per 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g per 24 hours or in the setting of nephrotic syndrome.

**Most Common Adverse Reactions—Combination With FOLFIRI**

- The most commonly reported adverse reactions (all grades; grade 3 or 4) occurring in ≥5% of patients receiving CYRAMZA plus FOLFIRI were proteinuria (15%) and gastrointestinal perforation (15%). In study 2, severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein/creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g per 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to ≤2 g per 24 hours. Permanently discontinue CYRAMZA for urine protein levels ≥3 g per 24 hours or in the setting of nephrotic syndrome.

**BRIEF SUMMARY:** For complete safety, please consult the full Prescribing Information.
INDICATIONS AND USAGE

Gastric Cancer

CYRAMZA as single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric cancer or gastric cancer-ESOPHAGEAL junction adenocarcinoma with disease progression on or after 5-FU or platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on or after platinum-based chemotherapy.

Non-Small Cell Lung Cancer

CYRAMZA in combination with docetaxel, is indicated for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on or after platinum-based chemotherapy.

Hemorrhage

Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In Study 3, the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticancer or chronic therapy with NSCLC or other antithrombotic therapy other than once daily aspirin or with radiographic evidence of major airway or vessel blood vessel invasion or intratumor cavitation were excluded from these studies. Before the risk of pulmonary hemorrhage in these groups of patients is unknown. In Study 3, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (4%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions

Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rashes/urticaria, back pain/axillae, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypotension, and anaphylaxis. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Gastrointestinal Perforation

CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In Study 2, the incidence of gastrointestinal perforations was also increased in patients that received CYRAMZA plus paclitaxel (11%) as compared to patients receiving placebo plus paclitaxel (3%). In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel and 0.3% for placebo plus docetaxel. In Study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or non-healing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Patients with Child-Pugh B or C Cirrhosis

Clinical deterioration, manifested by new or worsening ascites, encephalopathy, or hepatic encephalopathy was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported with a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

In Study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during therapy. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours or in the setting of nephrotic syndrome.

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In Study 3, the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticancer or chronic therapy with NSCLC or other antithrombotic therapy other than once daily aspirin or with radiographic evidence of major airway or vessel blood vessel invasion or intratumor cavitation were excluded from these studies. Before the risk of pulmonary hemorrhage in these groups of patients is unknown. In Study 3, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Disorders

Diabetes 14 1 9 2

Metabolism and Nutrition Disorders

Hypoglycemia 6 3 2 1

Nervous System Disorders

Headache 9 0 3 0

Vascular Disorders

Hypertension 16 8 8 3

Clinically relevant adverse reactions reported in ≤1% and ≤5% of CYRAMZA-treated patients in Study 1 were: neutropenia (4.7% CYRAMZA versus 0.9% placebo), anemia (4.7% CYRAMZA versus 0.9% placebo), rash (4.2% CYRAMZA versus 1.7% placebo), intestinal obstruction (2.1% CYRAMZA versus 0% placebo), and arterial thromboembolic events (1.7% CYRAMZA versus 0% placebo).

Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions.

In Study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in Study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

CYRAMZA Administered in Combination with Paclitaxel

Among 327 patients who received CYRAMZA (safety population) in Study 2, median age was 61 years, 31% were women, 63% were White, and 33% were Asian. Patients in Study 2 received a median of 9 doses of CYRAMZA; the median duration of exposure was 18 weeks, and 93 (28% of 327) patients received CYRAMZA for at least six months.

In Study 2, the most common adverse reactions (all grades) observed in patients treated with CYRAMZA plus paclitaxel at a rate of ≥5% and ≥2% higher than placebo plus paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. The most common laboratory abnormalities (all grades) observed in patients treated with CYRAMZA plus paclitaxel were anemia (3.1%) and increased bilirubin (2.8%). 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors. Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in Study 2 were neutropenia (4%) and thrombocytopenia (3%).

Table 2 provides the frequency and severity of adverse reactions in Study 2.

<table>
<thead>
<tr>
<th>Adverse Reactions (MedDRA) System Organ Class</th>
<th>CYRAMZA plus Paclitaxel (N=327)</th>
<th>Placebo plus Paclitaxel (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions (MedDRA) System Organ Class</td>
<td>All Grades (Frequency %)</td>
<td>Grade 3-4 (Frequency %)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Neutropenia</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>13</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhea</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal hemorrhage events</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
</tr>
</tbody>
</table>
Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in Study 2 were sepsis (3.1% CYRAMZA plus paclitaxel versus 1.8% placebo plus paclitaxel) and gastrointestinal perforations (1.2% CYRAMZA plus paclitaxel versus 0.3% for placebo plus paclitaxel).

Non-Small Cell Lung Cancer

CYRAMZA Administered in Combination with Docetaxel

Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m^2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m^2 intravenously every 3 weeks. Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 amended and 24% patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites received a starting dose of docetaxel at 60 mg/m^2 every 3 weeks. Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemoptysis within the preceding 2 months, and patients receiving therapeutic antiangiogenesis or chronic anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a lysine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor. The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0, 74% had no-squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 195 (31% of 627) patients received CYRAMZA for at least six months.

In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of ≥30% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue, neutropenia, and stomatitis/mucosal inflammation. Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infection-related reaction (0.5%) and epistaxis (0.3%). For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of ≥3 grade pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for ≥3 grade pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of ≥3 grade pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for ≥3 grade pulmonary hemorrhage for placebo plus docetaxel. The most common serious adverse events with CYRAMZA plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel. In patients ≥65 years, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients ≥65 years, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (8%) deaths for placebo plus docetaxel.

Table 3: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3

**Recommended Dose and Schedule**

CYRAMZA is administered as a 30-minute intravenous infusion over 30 minutes. Doses are administered once every 2 weeks. Continue CYRAMZA until disease progression or unacceptable toxicity.

**Dosage and Administration**

No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <1.5×ULN) hepatic impairment. However, due to the potential of CYRAMZA to increase the risk of vascular adverse events, patients with moderate hepatic impairment should be closely monitored for the development of vascular events.

**General Considerations**

Preparation of CYRAMZA for Administration

CYRAMZA is supplied as single-use vials containing 8 mg of ramucirumab per 0.3 mL volume (26.6 mg/mL). Each vial contains 2 mL 0.9% sodium chloride injection to provide a total volume of 2.3 mL. The vials contain no preservatives. CYRAMZA should be diluted with 2 mL of 0.9% sodium chloride injection, giving a final concentration of 3.9 mg/mL. Each vial should be used in sequence to maintain a concentration of at least 3.3 mg/mL. The vials are intended for single use only. The reconstituted solution should be used immediately after reconstitution.

**Contraindications**

• Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

**Warnings and Precautions**

• Infertility:

Advise females of reproductive potential regarding potential infertility effects of CYRAMZA.

• Lactation:

Advise patients not to breastfeed during CYRAMZA treatment.

• Respiratory, Thoracic, and Mediastinal Disorders

• Gastrointestinal Disorders

• Gastrointestinal and Administration Site Disorders

• General Disorders and Administration Site Disorders

**Drug Interactions**

No clinically significant interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and inotran or its active metabolite, SN-38.

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 86/2890 (3.0%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

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 incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

**Drug Interactions**

Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel-treated patients in Study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

**Colorectal Cancer**

CYRAMZA Administered in Combination with FOLFIRI

Study 4 was a multinational, randomized, double-blind study conducted in patients with metastatic colorectal cancer with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients received either CYRAMZA 8 mg/kg intravenously plus FOLFIRI intravenously every 2 weeks or placebo plus FOLFIRI intravenously every 2 weeks. Study 4 excluded patients with an ECOG PS of 2 or greater, uncontrolled hypertension, major surgery within 28 days, and those who experienced any of the following during first-line therapy with a bevacizumab-containing regimen: an arterial thromboembolic event, Grade 4 hypertension, Grade 3 proteinuria, or Grade 3-4 bleeding event, or bowel perforation.

Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 4

Table 2: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA plus Paclitaxel in Study 2 (Cont.)
USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. The background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-25%, respectively. Advise pregnant women of the potential risk to a fetus.

Animal Data

No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and feto-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

Lactation

Risk Summary

There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed-infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, CYRAMZA can cause fetal harm. Advise females of reproductive potential to use effective contraception while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Infertility

Females

Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use

The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondroplasty) at all doses tested (5–50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use

Of the 563 CYRAMZA-treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 1253 patients in Study 3, 465 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% Cl: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% Cl: 0.89, 1.36). Of the 529 patients who received CYRAMZA plus FOLFIRI in Study 4, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal Impairment

No dose adjustment is recommended for patients with renal impairment based on population pharmacokinetic analysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1.5 times ULN and any AST) or moderate (total bilirubin >3.0 times ULN and any AST) hepatic impairment based on population pharmacokinetic analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

DOSAGE AND ADMINISTRATION

Do not administer CYRAMZA as an intravenous push or bolus.

Recommended Dose and Schedule

Gastric Cancer

The recommended dose of CYRAMZA either as a single agent or in combination with weekly paclitaxel is 8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity. When given in combination, administer CYRAMZA prior to administration of paclitaxel.

Non-Small Cell Lung Cancer

The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity.

Colorectal Cancer

The recommended dose of CYRAMZA is 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration. Continue CYRAMZA until disease progression or unacceptable toxicity.

Premedication

Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H, antagonist (e.g., diphenhydramine hydrochloride).

For patients who have experienced a Grade 1 or 2 infusion-related reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion.

Dose Modifications

Infusion-Related Reactions (IRR)

• Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
• Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Hypertension

• Interrupt CYRAMZA for severe hypertension until controlled with medical management.
• Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

Proteinuria

• Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose (see Table 5) once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose (see Table 5) once the urine protein level returns to <2 g/24 hours.
• Permanently discontinue CYRAMZA for urine protein level ≥3 g/24 hours or in the setting of nephrotic syndrome.

Table 5: CYRAMZA Dose Reductions for Proteinuria

<table>
<thead>
<tr>
<th>Initial CYRAMZA Dose</th>
<th>First Dose Reduction to:</th>
<th>Second Dose Reduction to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg/kg</td>
<td>6 mg/kg</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>8 mg/kg</td>
<td>6 mg/kg</td>
</tr>
</tbody>
</table>

Wound Healing Complications

• Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed.

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

• Permanently discontinue CYRAMZA.

For toxicities related to paclitaxel, docetaxel, or the components of FOLFIRI, refer to the current prescribing information.

PATIENT COUNSELING INFORMATION

• Hemorrhage:

  Advise patients that CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadness.

• Arterial thromboembolic events:

  Advise patients of an increased risk of an arterial thromboembolic event.

• Hypertension:

  Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadness, or neurologic symptoms.

• Gastrointestinal perforations:

  Advise patients to notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain.

• Impaired wound healing:

  Advise patients that CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.

• Pregnancy and fetal harm:

  Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.

• Lactation:

  Advise patients not to breastfeed during CYRAMZA treatment.

• Infertility:

  Advise females of reproductive potential regarding potential infertility effects of CYRAMZA.

Additional information can be found at www.CYRAMZAHCPC.com.
Hepatic Infusion Can Convert CRC Liver Metastases to Operable State

by NANCY E. KEMENY, MD; MICHAEL I. D’ANGELICA, MD, FACS; AND JASHODEEP DATTA, MD

THE ADVENT OF HEPATIC ARTERIAL INFUSION (HAI) chemotherapy for treating patients with resectable colorectal liver metastases has increased survival outcomes to previously unimaginable levels. In 2017, findings from the largest retrospective study ever conducted to assess the impact of HAI in this population showed that the addition of this therapy extends survival by nearly 2 years. However, questions remain about the effectiveness of its use in patients with initially unresectable colorectal liver metastases.

In a review paper published online recently in JAMA Surgery, our team at Memorial Sloan Kettering (MSK) Cancer Center in New York, New York, provided a comprehensive overview of the role of HAI in this difficult-to-treat subset of patients. We discuss the biological rationale, the evolution of combining HAI with systemic chemotherapy, recent evidence for conversion to resection using HAI and systemic chemotherapy compared with systemic chemotherapy alone, and the toxicities and adverse effects (AEs) associated with HAI.

Overall, compelling response rates and rates of conversion to resection for patients with initially unresectable colorectal liver metastases treated with HAI suggest consideration of earlier initiation of the technique in chemotherapy-naïve patients as well as its adoption in patients who have failed first-line systemic chemotherapy before proceeding to second- or third-line regimens.

We pioneered HAI at MSK and have been continuously expanding and improving its clinical application for the past 30 years. We have generated most of the evidence to date supporting its use in patients with initially unresectable colorectal liver metastases. The broader oncology community is increasingly acknowledging its potential: Several North American centers have opened new HAI programs, and some new trials in progress may provide additional insights for improving patient outcomes even further.

THE BIOLOGICAL RATIONALE FOR HAI
Colorectal cancer (CRC) is the third most common cancer in the United States, accounting for an estimated 145,600 new cases and 51,000 deaths in 2019. More than half of patients with CRC develop liver metastases. Five-year overall survival (OS) exceeds 50% for select MSK patients with limited colorectal liver metastases who undergo complete resection. Most patients experience recurrence after hepatectomy, but about 20% are cured after resection on long-term follow-up in our series.

Resection is the primary contributor to long-term survival, but only 15% to 20% of patients with colorectal liver metastases present with resectable metastases. Major work in the field has focused on converting more patients to resection. Newer systemic therapies have been transformative for downstaging patients from having initially inoperable liver metastases to potentially resectable liver metastases. These therapies include irinotecan and oxaliplatin as well as the combination regimens FOLFOX (leucovorin, fluorouracil, and oxaliplatin), FOLFIRI (leucovorin, fluorouracil, and irinotecan), and FOLFOXIRI (fluorouracil, oxaliplatin, and irinotecan), with or without agents that target EGFR or VEGF.

However, modern chemotherapy rarely cures patients with initially unresectable colorectal metastases or those with extrahepatic disease. For those patients, median survival is 22 months to 24 months, median progression-free survival (PFS) is 10 months, and response rates in the second-line setting are only 10% to 30%.

Since the hepatic artery carries the main blood supply to liver metastases, we can deliver agents with high first-pass hepatic extraction directly to tumors via HAI while sparing healthy liver tissue by perfusing the agents, mainly through portal circulation. HAI is typically administered via the gastroduodenal artery through a surgically implanted pump, hepatic...
arterial port, or percutaneous catheter connected to an external pump. Limiting systemic toxic effects with HAI also means that we can treat patients concurrently with systemic chemotherapies at near-full doses. The most common AE from HAI of floxuridine is hepatic enzyme elevation and, rarely, biliary sclerosis. To decrease hepatic toxicity, we administer dexamethasone in the pump and adjust doses appropriately. Irinotecan and oxaliplatin have also been used in HAI, mostly in Europe and Asia.

**COMBINING HAI WITH SYSTEMIC CHEMOTHERAPY**

Between January 1996 and December 2000, the multicenter Cancer and Leukemia Group B 9481 trial compared HAI alone with systemic chemotherapy alone. The trial randomized 135 patients with initially unresectable colorectal liver metastases to receive either HAI consisting of floxuridine and leucovorin or systemic bolus fluorouracil and leucovorin.

The HAI group fared significantly better than the systemic chemotherapy group, with a longer median OS of 24.4 months versus 20.0 months ($P = .003$), a response rate of 47% versus 24%, and time to hepatic progression of 9.8 months versus 7.3 months, respectively. However, patients in the HAI group had a significantly shorter time to extrahepatic progression: 7.7 months versus 14.8 months for the systemic chemotherapy group.

The results of this trial generated lively debate about the relevance of HAI alone in patients with initially unresectable colorectal liver metastases. However, by the time of its publication in 2006, most institutions had already moved on to use HAI in combination with systemic chemotherapies, and several phase I and phase II trials were underway.

The approval of oxaliplatin and irinotecan in the late 1990s led to the next generation of HAI trials testing combination regimens. For example, a phase I trial at MSK tested HAI of floxuridine combined with 2 separate oxaliplatin-based therapies, irinotecan or fluorouracil and leucovorin, in 36 patients who progressed on first-line chemotherapy. Response rates approached 90% in both groups; median OS was 36 months for the irinotecan group and 22 months for the fluorouracil and leucovorin group.

A separate phase I trial at MSK was among the first prospective studies to examine the effectiveness of HAI in converting initially unresectable colorectal liver metastases to resectable or abatable disease. Forty-nine patients received HAI of floxuridine with oxaliplatin and irinotecan. The response rate was 92% in this heavily pretreated patient population, Kemeny and colleagues reported. Median OS was 51 months for patients who were chemotherapy naïve and 35 months for those who had been treated previously. Systemic options are limited to investigational agents, such as regorafenib (Stivarga) and TAS-102 (trifluridine/tipiracil; Lonsurf), for patients with initially unresectable colorectal liver metastases who progress on standard chemotherapies, but these agents produce response rates of only 1% to 2%. However, HAI is a viable salvage approach for controlling disease in these patients.

At MSK, we examined results for 110 patients with initially unresectable colorectal liver metastases who were refractory to fluorouracil with leucovorin, irinotecan, and oxaliplatin with or without bevacizumab (Avastin) or anti-EGFR therapy, and who were then treated with HAI of floxuridine and best systemic therapy. The response rate was 35%–a rate that is not possible with systemic chemotherapy alone in refractory patients.

Discoveries of some of the molecular drivers of disease have led to investigations of combining systemic chemotherapy with HAI, with or without targeted therapies, such as anti-EGFR agents for RAS wild-type mutations and anti-VEGF agents. However, efforts targeting the molecular characteristics of initially unresectable colorectal liver metastases are still in early stages.

**EFFECTIVENESS OF HAI TO CONVERT INITIALLY UNRESECTABLE COLORECTAL LIVER METASTASES TO RESSECTION**

The primary goal of multimodal treatment for initially unresectable colorectal liver metastases is to optimize response to make resection possible. Research has shown that patients whose disease can be converted to resection fare as well as those whose disease was resectable up front.

Kemeny and colleagues examined the effectiveness of HAI in converting initially unresectable colorectal liver metastases to resectable or abatable disease in 49 patients. Conversion to resection was achieved in 47% of patients overall and 57% of those who were chemotherapy naïve. Despite a substantial burden of disease among these patients, and a strict definition of irresectability, the response rate was 76%. Conversion to resection was the only factor independently associated with prolonged OS and PFS. Three-year OS rates were an astonishing 80% for patients who underwent hepatectomy compared with only 26% for those whose disease remained inoperable.

MSK investigators recently updated this trial’s results with longitudinal data from an expanded cohort of 64 patients. At a median follow-up of 86 months, 52% of patients had achieved conversion to resection, a rate more than 2 times greater than the historical average. Median PFS was 13 months, and median OS was 38 months, with a 5-year OS of 36%.

Outcomes were significantly better for chemotherapy-naïve patients compared with those who had been treated previously: Response rates were 86% versus 61%, PFS was 19.7 months versus 10.0 months, and median OS was 76.6 months versus 29.7 months, respectively. Only conversion to resection was significantly associated with OS on multivariate analysis. The approach also demonstrated curative potential: Nine patients (14%) were disease free at about 5 years of follow-up.
MANAGING TOXICITIES AND ADVERSE EFFECTS

It is essential to balance our enthusiasm for liver-directed therapy with an awareness of the toxic effects of this treatment. Allen and colleagues found that 544 patients (22%) treated at MSK from 1986 to 2001 experienced complications. The incidence of complications decreased with surgical experience. Most issues were salvageable, with 80% of pumps functioning for at least 2 years.37

A review of drug-related toxic effects from HAI in 4580 patients treated at MSK found gastrointestinal symptoms in 25%, hepatic toxic effects in 22%, and myelosuppression in 9%. HAI of floxuridine was mainly associated with hepatic enzyme elevations, which lead to biliary sclerosis in some people.38

Another MSK study found that 4.6% of patients undergoing HAI of floxuridine required a stent, and yet there was no difference in survival between those who received salvage treatment with a stent and dilation compared with patients without biliary complications.39 A further study among 50 randomized patients found a higher dose tolerance of floxuridine at 5 months ($P = .05$) with concurrent administration of dexamethasone.40

ADVANCING THE TREATMENT OF COLORECTAL LIVER METASTASES

Determining up front whether we can resect patients’ metastases requires technical expertise gained in a high-volume institution in a setting of multidisciplinary oncologic care. Further, administering HAI is complex and requires a dedicated team of surgeons, oncologists, radiologists, and nurses to ensure that patients achieve the best outcomes possible.

At MSK, we have pioneered the use of HAI in initially unresectable colorectal liver metastases and generated a substantial portion of the evidence in the field to date. We are currently conducting a randomized phase II study (NCT01312857) of HAI of floxuridine and dexamethasone and intravenous irinotecan, 5-fluorouracil, and leucovorin, with or without the anti-EGFR agent panitumumab (Vectibix), in patients with wild-type KRAS and resected liver metastases.

We are also excited to see results from a phase III trial (NCT02102789) by Chinese investigators who are comparing HAI of floxuridine plus modified FOLFOX6 and dexamethasone versus modified FOLFOX6 alone, with a primary outcome of margin-negative resection. This study may finally answer the question about the effectiveness of HAI plus systemic chemotherapy compared with systemic chemotherapy alone.

We look forward to future advances in the field, including refining patient selection, learning more about the genetic determinants of response, incorporating targeted therapies into rational trial design, and developing multi-institutional registries comparing outcomes for current and alternative liver-directed treatment approaches.
When everyone looked for a way out, we went in.

During Hurricane Harvey, we worked diligently to make sure our customers remained compliant. No one else can provide the expertise and assurance that your facility is serviced without interruption during times of crisis.

Stericycle.com/Partnership for more information.
AN UPDATED ANALYSIS OF patients with NTRK fusion–positive non-small cell lung cancer (NSCLC), including patients with central nervous system (CNS) metastases, showed that the TRK inhibitor larotrectinib (Vitrakvi) demonstrates significant activity in this population, validating the strategy of oncogenes in the malignancy, according to Anna F. Farago, MD, PhD.

Larotrectinib became the second tissue-agnostic therapy to gain the FDA’s approval for the treatment of patients with cancer in November 2018, following the agency’s decision to grant an indication for pembrolizumab (Keytruda) in unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumors.1,2

The FDA granted an accelerated approval to larotrectinib for the treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or for whom surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or whose disease has progressed following treatment.

In August, the FDA approved entrectinib (Rozlytrek) for patients with NTRK fusion-positive solid tumors and for those with ROS1-positive NSCLC. Entrectinib inhibits TRK kinases encoded by NTRK genes as well as ROS1, ALK, and other kinases.3

The efficacy of larotrectinib was demonstrated in previous phase II data from the NAVIGATE trial (NCT02576431) involving adults and children with NTRK fusion–positive solid tumors, and in a prior phase I study (NCT02122913) that assessed the safety of larotrectinib in cancers in adults that harbored an NTRK fusion.

In the updated results of these studies, specifically of patients with advanced NTRK fusion–positive NSCLC, investigators found that larotrectinib is highly active, including in those with CNS metastases. Its safety profile was favorable as well (TABLE).4

Farago, who presented the findings during the 2019 World Conference on Lung Cancer, discussed the implications of the new data. She is an assistant professor of medicine at Harvard Medical School in Boston, Massachusetts.

“...What is striking is that larotrectinib has activity in a tumor-agnostic manner, so regardless of the tumor type, if an NTRK fusion is present, it tends to act as an oncogenic driver. It also predicts a high likelihood of response to larotrectinib.”

—ANNA F. FARAGO, MD, PhD

Q: Please discuss the analysis of larotrectinib in NSCLC.

The data that I presented looked at patients with NSCLC harboring an NTRK gene fusion and outcomes for those patients who were treated with larotrectinib, which is a selective TRK inhibitor.

Generally, patients with NSCLC who do not have a targetable oncogenic driver are treated with chemotherapy, or chemotherapy plus immunotherapy, or sometimes single-agent immunotherapy. We see a range of responses and durability of responses to treatment.

Based on many studies in EGFR-mutant lung cancers, ALK-fusion lung cancers, and ROSI-positive lung cancer, we know that patients who have a targetable oncogenic driver do much better with targeted therapies than they do with traditional chemotherapy. That has been shown...
in randomized studies in EGFR- and ALK-positive lung cancers.

NTRK fusion–positive lung cancers are a much smaller population. We estimate that NTRK fusions occur in 0.2% of all lung cancers, so these are very uncommon events. It would be very hard to imagine putting together a randomized study where you’re comparing outcomes with chemotherapy versus a targeted TRK inhibitor in patients with this alteration because it’s such a small population.

**Q:** What new data are presented in this analysis?

We now have single-arm data for outcomes in patients with an NTRK fusion who were treated with larotrectinib, and the results are very encouraging. What the data show is that larotrectinib is highly active in this population, which is very consistent with what we’ve seen with targeted therapies for other oncogenic drivers in lung cancer. We saw a response rate of 75% among 12 patients with NTRK fusion–positive lung cancer who were treated with larotrectinib. Among those, 6 patients had brain metastases and 4 of those had partial responses to larotrectinib, for a response rate of 67%.

We don’t have a head-to-head comparison to tell us that it’s definitely better than chemotherapy, but we can extrapolate from everything we know based on other oncogene-driven cancers that targeted therapy is the option for these patients.

**Q:** What is the impact of the approval of larotrectinib for patients with lung cancer?

Larotrectinib was approved by the FDA at the end of 2018, based on data across a wide number of cancer types, showing an overall response rate of 81% among those patients with NTRK gene fusions. What is striking is that larotrectinib has activity in a tumor-agnostic manner, so regardless of the tumor type, if an NTRK fusion is present, it tends to act as an oncogenic driver. It also predicts a high likelihood of response to larotrectinib.

It’s exciting to have an approval by the FDA for a targeted therapy in a tumor-agnostic manner. Also, this approval doesn’t just impact lung cancer, it impacts all solid tumors because we see these fusions across solid tumors. They are uncommon events in most cancer types. In lung cancer the frequency is about 0.2%; proportionally, however, there are a lot of patients with lung cancer as a general population. Therefore, numerically, a fair number of people could potentially benefit from this drug in the lung cancer community.

Looking at other cancer types, there’s a variable incidence of NTRK fusions. They can be quite common in some rare cancer types, such as infantile fibrosarcoma or mammary analogue secretory carcinoma. However, because they can occur in any cancer type, we need to be looking for NTRK gene fusions, regardless of the cancer tissue of origin. And, if these fusions are identified, then larotrectinib represents an exciting treatment option for patients.

**Q:** What other agents are showing promise for targeting NTRK fusions?

In lung cancer specifically, we’re already routinely screening patients for gene alterations in EGFR, ALK, and ROS1. We should be [testing for] RET and making the case for BRAF, NRG1, and others. Adding NTRK to a gene fusion panel shouldn’t be too much of a burden for people. We should be asking our molecular pathologists or our commercial vendors to be adding NTRK to their panels if it’s not already included. It’s not practical to screen for NTRK fusions only in this population, because those are such rare events. But it is practical to screen for all of these eventssimultaneously using a multigene next-generation sequencing-based assay.

**Q:** What should oncologists take away from these data?

In lung cancer, we now see a growing number of somatic alterations that are potentially treatable with highly active targeted therapies. These alterations include EGFR, ALK, ROS1, RET, NTRK, and BRAF. All patients with advanced or metastatic NSCLC should undergo testing with broad multiplexed [assay] to look at all of these mutations simultaneously at the time of diagnosis so that we can identify these patients early and direct them to the appropriate targeted therapy.

**REFERENCES**


INDICATION
KYPROLIS® is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION
FOR KYPROLIS

Cardiac Toxicities
New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejec tion fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of administration.

Monitor patients for signs or symptoms of cardiac failure or ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart at 1 dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate.

For patients >75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, anemia, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Acute Renal Failure
Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency adverse events (including renal failure) have occurred. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome
Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred. Patients with a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, and withhold until resolved.

Pulmonary Toxicity
Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension
Pulmonary arterial hypertension (PAH) was reported. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart based on a benefit/risk assessment.

Dyspnea
Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart based on a benefit/risk assessment.

Hypertension
Hypertension, including hypertensive crisis and hypertensive emergency, has been observed, some fatal. Control hypertension prior to starting KYPROLIS. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart based on a benefit/risk assessment.

Venous Thrombosis
Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient’s underlying risks.
**Acute Renal Failure**

- Monitor patients for signs or symptoms of cardiac failure or ischemia.
- Evaluate new onset or worsening of pre-existing cardiac failure (e.g., congestive failure was reported more frequently in patients with advanced relapsed and insufficient adverse events (including renal failure) have occurred. Acute renal risk for cardiac complications and should have a comprehensive medical New York Heart Association Class III and IV heart failure, recent myocardial failure. Adjust total fluid intake as clinically appropriate.
- Promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or cardiac arrest has occurred within one day of administration.
- Fatalities have occurred following administration of KYPROLIS. Some events cardiomyopathy, myocardial ischemia, and myocardial infarction including.

**Indications**

- Venous thromboembolic events (including deep venous thrombosis hypertension
- Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea
- Pulmonary arterial hypertension (PAH) was reported. Evaluate with cardiac
- Pulmonary Hypertension
- Tumor Lysis Syndrome
- Venous Thrombosis
- Hypertension
- Hemorrhage
- Thrombocytopenia
- Hepatic Toxicity and Hepatic Failure
- Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients
- Embryo-fetal Toxicity
- Thrombotic Microangiopathy
- Posterior Reversible Encephalopathy Syndrome (PRES)

**CHOOSE THE DOSE THAT BEST MEETS YOUR PATIENT’S NEEDS**

<table>
<thead>
<tr>
<th>IMID-CONTAINING</th>
<th>IMID-FREE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRd27 TWICE WEEKLY</strong></td>
<td><strong>Kd56 TWICE WEEKLY</strong></td>
</tr>
<tr>
<td>10 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>KYPROLIS® priming dose</td>
<td>20 mg/m² Days 1 and 2 of Cycle 1 to evaluate tolerability</td>
</tr>
<tr>
<td>Target KYPROLIS® therapeutic dose</td>
<td>56 mg/m² starting Day 8 of Cycle 1</td>
</tr>
<tr>
<td>Treatment schedule</td>
<td>• Administer 56 mg/m² 2 consecutive days each wk for 3 wks • Continue until disease progression or unacceptable toxicity occurs • Discontinue KYPROLIS® after Cycle 1</td>
</tr>
<tr>
<td><strong>Kd70 ONCE WEEKLY</strong></td>
<td><strong>Kd70 ONCE WEEKLY</strong></td>
</tr>
<tr>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>KYPROLIS® priming dose</td>
<td>20 mg/m² Day 1 of Cycle 1 to evaluate tolerability</td>
</tr>
<tr>
<td>Target KYPROLIS® therapeutic dose</td>
<td>56 mg/m² starting Day 8 of Cycle 1</td>
</tr>
<tr>
<td>Treatment schedule</td>
<td>• Administer 70 mg/m² 1 day each wk for 3 wks • Follow with 13-day rest period, as part of 28-day tx cycle • For Cycles 10 and beyond, dexamethasone is not given on Day 22</td>
</tr>
</tbody>
</table>

Refer to lenalidomide and/or dexamethasone Prescribing Information.

**MANAGE HYDRATION THROUGHOUT TREATMENT:**

- Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity.
- The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and IV fluids (250 mL to 500 mL of appropriate IV fluid prior to each dose in Cycle 1)
- If needed, give an additional 250 mL to 500 mL of IV fluids following KYPROLIS® administration
- Continue oral and/or IV hydration, as needed, in subsequent cycles
- Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure

**IMiD = immunomodulatory drugs; Kd = KYPROLIS®+dexamethasone; KRd = KYPROLIS®+lenalidomide and dexamethasone; wk = week; wks = weeks; tx = treatment; IV = intravenous.

- Patients using hormonal contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment.
- Infusion Reactions
  - Infusion reactions, including life-threatening reactions, have occurred. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomit, weakness, shortness of breath, hypotension, syncope, chest tightness, or anemia. These reactions can occur immediately following or up to 24 hours after administration. Premedicate with dexamethasone to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and seek immediate medical attention if they occur.
- Hemorrhage
  - Fatal or serious cases of hemorrhage have been reported. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.
- Thrombocytopenia
  - KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Monitor platelet counts frequently during treatment. Reduce or withhold dose as appropriate.
- Hepatic Toxicity and Hepatic Failure
  - Cases of hepatic failure, including fatal cases, have occurred. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.
- Thrombotic Microangiopathy
  - Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred. Monitor for signs and symptoms of TTP/HUS. Discontinue if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS is not known.
- Posterior Reversible Encephalopathy Syndrome (PRES)
  - Cases of PRES have occurred in patients receiving KYPROLIS. If PRES is suspected, discontinue and evaluate with appropriate imaging. The safety of reinitiating KYPROLIS is not known.

**Informed by Therapeutic and Priming Dosing**

- 20 mg/m² Days 1 and 2 of Cycle 1 to evaluate tolerability
- 56 mg/m² starting Day 8 of Cycle 1
- 20 mg/m² Day 1 of Cycle 1 to evaluate tolerability
- 70 mg/m² starting Day 8 of Cycle 1

**Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients**

- In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse events was observed in patients in the KMP arm. KMP is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

**Embryo-fetal Toxicity**

- KYPROLIS can cause fetal harm when administered to a pregnant woman.
- Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS and for 6 months following the final dose. Males of reproductive potential should be advised to avoid fathering a child while being treated with KYPROLIS and for 3 months following the final dose. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus.

**ADVERSE REACTIONS**

- The most common adverse reactions in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

**Please see Brief Summary of full Prescribing Information on adjacent pages.**

Reference: KYPROLIS® (carfilzomib) prescribing information, Onyx Pharmaceuticals Inc., an Amgen Inc. subsidiary.

**LEARN MORE AT** KYPRLIS-HCP.COM

© 2019 Amgen Inc. All rights reserved. USA-171-80635 Printed in USA
KYPROLIS® (carfilzomib) for injection, for intravenous use
Brief Summary of Prescribing Information.
Please see the KYPROLIS package insert for full prescribing information.

INDICATIONS AND USAGE

• Kyprolis is indicated in combination with dexamethasone or with lenalidomide for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

WARNINGS AND PRECAUTIONS

Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis administration. In randomized, open-label, multicenter trials for combination therapies, the incidence of cardiac failure events was 8%.

Monitor patients for cardiac signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart Kyprolis at a dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.

In patients ≥75 years of age, the risk of cardiac failure is increased compared to patients <75 years of age. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure control and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up.

Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Kyprolis. Some of these events have been fatal. Renal insufficiency adverse events (including renal failure) have occurred in approximately 11% of patients treated with Kyprolis. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. The baseline estimated glomerular filtration rate (eGFR) was less than 60 mL/min/1.73 m² in 23% of patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in Cycle 1, and in subsequent cycles as needed. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, including interruption of Kyprolis until TLS is resolved.

Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in approximately 1% of patients receiving Kyprolis. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue Kyprolis.

Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 1% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline, and consider whether to restart Kyprolis based on a benefit/risk assessment.

Dyspnea

Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 5 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment.

Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating KRd versus Rd, the incidence of hypertension events was 17% in the KRd arm versus 9% in the Rd arm. In a randomized, open-label, multicenter trial of KD versus Vd, the incidence of hypertension events was 34% in the Kd arm versus 11% in the Vd arm. Some of these events have been fatal. It is recommended to control hypertension prior to starting Kyprolis. Monitor blood pressure regularly in all patients while on Kyprolis. If hypertension cannot be adequately controlled, withhold Kyprolis and prednisone. Consider whether to restart Kyprolis based on a benefit/risk assessment.

Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating KRd versus Rd with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm versus 6% in the Rd arm. In a randomized, open-label, multicenter trial of KD versus Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm versus 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%.

Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient’s underlying risk.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone.

Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion reactions. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with Kyprolis. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous, and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 32% of patients in clinical trials with Kyprolis. Monitor platelet counts frequently during treatment with Kyprolis. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (<1%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases. Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. If the diagnosis of TTP/HUS is excluded, Kyprolis may be restarted.

The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI).

Discontinue Kyprolis if PRES is suspected and evaluate. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients

In a clinical trial of 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomized to Kyprolis (20/36 mg/m2 by 30-minute infusion twice weekly for four of each six-week cycle), melphalan, and prednisone (KMP) or bortezomib, melphalan, and prednisone (VMP), a higher incidence of fatal adverse reactions (7% versus 4%) and serious adverse reactions (50% versus 42%) were observed in the KMP arm compared to patients in the VMP arm, respectively. Patients in the KMP arm were observed to have a higher incidence of any grade adverse reactions involving cardiac failure (11% versus 4%), hypertension (20% versus 8%), acute renal failure (14% versus 6%), and dyspnea (18% versus 9%). This study did not meet its primary outcome measure of superiority in progression-free survival (PFS) for the KMP arm. Kyprolis in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.
Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, Kyprolis can cause fetal harm when administered to a pregnant woman. Carfilzomib administered intravenously to pregnant rabbits during organogenesis at a dose approximately 40% of the clinical dose of 27 mg/m² based on body surface area caused post-implantation loss and a decrease in fetal weight.

Females of reproductive potential should avoid becoming pregnant while being treated with Kyprolis. Advise females of reproductive potential that they must use contraception during treatment with Kyprolis and for 6 months following the final dose. Advise males with sexual partners of reproductive potential that they must use contraception during treatment with Kyprolis and for 3 months following the final dose. If Kyprolis is used during pregnancy or if the patient becomes pregnant during Kyprolis treatment, the patient should be apprised of the potential risk to the fetus.

ADVERSE REACTIONS

The following adverse reactions have been discussed above and can be found in the Warnings and Precautions section of the prescribing information. They include Cardiac Toxicities, Acute Renal Failure, TLS, Pulmonary Toxicity, Pulmonary Hypertension, Dyspnea, Hypertension, Venous Thrombosis, Infusion Reactions, Hemorrhage, Thrombocytopenia, Hepatic Toxicity and Hepatic Failure, Thrombotic Microangiopathy, PRES, and Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients.

Clinical Trials Experience

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

Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRD) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. The median number of cycles initiated was 22 cycles for the KRD arm and 14 cycles for the Rd arm. Deaths due to adverse reactions within 30 days of the last dose of any therapy in the KRD arm occurred in 45/392 (11%) patients compared with 42/389 (11%) patients who died due to adverse reactions within 30 days of the last dose of any therapy. The most common cause of death occurring in patients (%) in the two arms (KRD vs Rd) included infection 12 (3%) versus 11 (3%), cardiac 10 (3%) versus 9 (2%), and other adverse reactions 23 (6%) versus 22 (6%). Serious adverse reactions were reported in 65% of the patients in the KRD arm and 57% of the patients in the Rd arm. The most common serious adverse reactions reported in the KRD arm as compared with the Rd arm were pneumonia (17% vs. 13%), respiratory tract infection (4% vs. 2%), pyrexia (4% vs. 3%), and pulmonary embolism (2% vs. 2%). In patients treated with Kyprolis, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 57% in patients <65 years of age, 73% in patients 65 to 74 years of age, and 81% in patients >75 years of age. Discontinuation due to any adverse reaction occurred in 33% in the KRD arm versus 30% in the Rd arm. Adverse reactions leading to discontinuation of Kyprolis occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%). The incidences of cardiac failure events was 7% in the KRD arm versus 4% in the Rd arm.

Most Common Adverse Reactions (≥10%) in the KRD Arm

Occurring in Cycles 1–12 (20/27 mg/m² Regimen in Combination with Lenalidomide and Dexamethasone)

<table>
<thead>
<tr>
<th>Adverse Reactions by Body System</th>
<th>KRD Arm (N = 392), n (%)</th>
<th>Rd Arm (N = 389), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>≥ Grade 3</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>138 (35)</td>
<td>53 (14) 127 (33) 47 (12)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>124 (32)</td>
<td>104 (27) 115 (30) 89 (23)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>100 (26)</td>
<td>58 (15) 75 (19) 39 (10)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>119 (30)</td>
<td>8 (2) 106 (27) 12 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>68 (17)</td>
<td>0 (0) 55 (14) 1 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>63 (16)</td>
<td>1 (0) 43 (11) 3 (1)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (29)</td>
<td>23 (6) 107 (28) 20 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>93 (24)</td>
<td>5 (1) 64 (17) 1 (0)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>59 (15)</td>
<td>3 (1) 48 (12) 2 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>54 (14)</td>
<td>11 (3) 49 (13) 7 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infections and Infestations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>87 (22)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>55 (14)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>55 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>54 (14)</td>
<td>35 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and Nutrition Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>78 (20)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>55 (14)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>43 (11)</td>
<td>18 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and Connective Tissue Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasms</td>
<td>92 (24)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>41 (11)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous System Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathies</td>
<td>43 (11)</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>64 (16)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, Thoracic, and Mediastinal Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>93 (24)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>71 (18)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and Subcutaneous Tissue Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>45 (12)</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular Disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic and thrombotic events</td>
<td>49 (13)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (11)</td>
<td>12 (3)</td>
</tr>
</tbody>
</table>

KRD = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone.

- Pneumonia includes pneumonia and bronchopneumonia.
- Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.
- Cough includes cough and productive cough.
- Dyspnea includes dyspnea and dyspnea exertional.
- Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.
- Hypertension includes hypertension, hypertensive crisis.

There were 274 (70%) patients in the KRD arm who received treatment beyond Cycle 12. There were no new clinically relevant adverse reactions that emerged in the later treatment cycles.

Adverse Reactions Occurring at a Frequency of < 10%:

- Blood and lymphatic system disorders: febrile neutropenia, lymphopenia
- Cardiac disorders: cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, pericardial effusion
- Ear and labyrinth disorders: deafness, tinnitus
- Eye disorders: cataract, vision blurred
- Gastrointestinal disorders: abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- General disorders and administration site conditions: chills, infusion site reaction, multi-organ failure, pain
- Infections and infestations: clostridium difficile colitis, influenza, lung infection, pneumonitis, sepsis, urinary tract infection, viral infection
- Metabolism and nutrition disorders: dehydration, hyperkalemia, hyperuricemia, hyperalbuminemia, hypernatremia, tumor lysis syndrome
- Musculoskeletal and connective tissue disorders: muscular weakness, myalgia
- Nervous system disorders: hypoesthesia, intracranial hemorrhage, paresthesia
- Psychiatric disorders: anxiety, delirium
- Renal and urinary disorders: renal failure, renal failure acute, renal impairment
- Respiratory, thoracic and mediastinal disorders: dyspnoea, epistaxis, oropharyngeal pain, pulmonary embolism, pulmonary edema, pulmonary hemorrhage
- Skin and subcutaneous tissue disorders: erythema, hyperhidrosis, pruritus
- Vascular disorders: deep vein thrombosis, hemorrhage, hypertension

Grade 3 and higher adverse reactions that occurred during Cycles 1–12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.
Laboratory Abnormalities
Table 10 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the Kd arm for patients who received combination therapy.

Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma
The safety of Kyprolis in combination with dexamethasone was evaluated in two open-label, randomized trials (ENDEAVOR and A.R.R.O.W.).

ENDOEVAR evaluated patients with relapsed or refractory multiple myeloma. Patients received treatment for a median duration of 48 weeks in the twice weekly Kyprolis/dexamethasone (Kd) 20/56 mg/m² arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm. Deaths due to adverse reactions within 30 days of last study treatment occurred in 32/463 (7%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd vs. Vd) included cardiac 4 (1%) versus 5 (1%), infections 9 (2%) versus 8 (2%), disease progression 7 (2%) versus 4 (1%), pulmonary 3 (1%) versus 2 (<1%), renal 1 (<1%) versus 0 (0%), and other adverse events 9 (2%) versus 2 (<1%). Serious adverse reactions were reported in 59% of the patients in the Kd arm and 40% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (8% vs. 9%). In patients treated with Kyprolis, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 54% in patients <65 years of age, 60% in patients 65 to 74 years of age, and 69% in patients ≥75 years of age. Discontinuation due to any adverse reaction occurred in 15% (Kd vs. Vd) versus 26% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 8, 2%) and peripheral neuropathy in the Vd arm (n = 22, 5%). The incidence of cardiac failure events was 11% in the Kd arm versus 3% in the Vd arm.

Most Common Adverse Reactions (≥ 10% in either Kd Arm)

<table>
<thead>
<tr>
<th>Adverse Reaction by Body System</th>
<th>Kd (N = 463), n (%)</th>
<th>Vd (N = 456), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Any Grade</td>
<td>≥ Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>161 (35)</td>
<td>112 (25)</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>125 (27)</td>
<td>112 (25)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>117 (25)</td>
<td>149 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (5)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>60 (13)</td>
<td>113 (25)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45 (10)</td>
<td>5 (1)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>28 (6)</td>
<td>162 (29)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>162 (22)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 (15)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>6 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>55 (12)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>54 (12)</td>
<td>5 (1)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>70 (15)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>64 (14)</td>
<td>63 (13)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Peripheral neuropathies*</td>
<td>56 (12)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>105 (23)</td>
<td>116 (25)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>123 (27)</td>
<td>66 (15)</td>
</tr>
<tr>
<td>Cough*</td>
<td>97 (21)</td>
<td>6 (1)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>83 (18)</td>
<td>30 (7)</td>
</tr>
</tbody>
</table>

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone.

*Thrombocytopenia includes platelet count decreased and thrombocytopenia.
Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.
Dyspnea includes dyspnea and dyspnea exertional.
Cough includes cough and productive cough.
Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency. The event rate of ≥ Grade 2 peripheral neuropathy in the Kd arm was 7% (95% CI: 5.9–9.3%) versus 35% (95% CI: 31.9–38.9%) in the Vd arm.

Adverse Reactions Occurring at a Frequency of <10%

**Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, lymphopenia, neutopenia, thrombotic microangiopathy, thrombotic thrombocytopenic purpura.
**Cardiac disorders:** atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, palpitations, tachycardia.
**Ear and labyrinth disorders:** tinnitus.
**Eye disorders:** cataract, vision blurred.
**Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, tachyphasia.
**General disorders and administration site conditions:** chest pain, chills, influenza-like illness, infusion site reactions (including inflammation, pain, and erythema), malaise, pain.
**Hepatobiliary disorders:** cholestasis, hepatic failure, hepatobiliary necrosis.
**Immunosuppressive disorders:** drug hypersensitivity.
**Infections and infestations:** bronchopneumonia, gastroenteritis, influenza, lung infection, nasopharyngitis, pneumonia, rhinitis, sepsis, urinary tract infection, viral infection.
**Metabolism and nutrition disorders:** decreased appetite, dehydration, hypercalcemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalemia, hypomagnesemia, hypophosphatemia, tumor lysis syndrome.
**Musculoskeletal and connective tissue disorders:** muscular weakness, muscle pain, myalgia.
**Nervous system disorders:** cerebrovascular accident, dizziness, hypotension, paresthesia, posterior reversible encephalopathy syndrome.
**Psychiatric disorders:** anxiety.
**Renal and urinary disorders:** renal failure, renal failure acute, renal impairment.
**Respiratory, thoracic and mediastinal disorders:** acute respiratory distress syndrome, dysphonia, epistaxis, interstitial lung disease, oropharyngeal pain, pneumonitis pulmonary embolism, pulmonary edema, pulmonary hypertension, wheezing.
**Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash.
**Vascular disorders:** deep vein thrombosis, flushing, hypotension.

A.R.R.O.W. evaluated patients with relapsed and refractory multiple myeloma. Patients received treatment for a median duration of 36 weeks in the once weekly Kd 20/70 mg/m² arm and 23.1 weeks in the twice weekly Kd 20/27 mg/m² arm of A.R.R.O.W. The safety profile for the once weekly Kd 20/70 mg/m² regimen was similar to the twice weekly Kd 20/27 mg/m² regimen.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 72/235 (31%) patients in the Kd arm and 9/235 (4%) patients in the Kd 20/27 mg/m² arm. The most frequent fatal adverse reactions occurring in patients (%) in the two arms (once weekly Kd 20/70 mg/m² versus twice weekly Kd 20/27 mg/m²) were sepsis (1% versus 2% <1%), septic shock (1% versus 1% <1%), and infection (1% versus 0% 0%). Serious adverse reactions were reported in 43% of the patients in the Kd 20/70 mg/m² arm and 41% of the patients in the Kd 20/27 mg/m² arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% versus 7%). In patients treated with once weekly Kd 20/70 mg/m², 57% were 65 and over and 19% were 75 and over. The incidence of serious adverse events was 37% in patients <65 years of age, 50% in patients 65 to 74 years of age, and 44% in patients ≥75 years of age. Discontinuation due to any adverse reaction occurred in 13% in the Kd 20/70 mg/m² arm versus 12% in the Kd 20/27 mg/m² arm. The most common reaction leading to discontinuation was acute kidney injury (2% versus 2%). The incidence of cardiac failure events was 3.8% in the once weekly Kd 20/70 mg/m² arm versus 5.1% in the twice weekly Kd 20/27 mg/m² arm.

Most Common Adverse Reactions (≥ 10% in either Kd Arm)

Adverse Reactions by Body System

<table>
<thead>
<tr>
<th>Adverse Reaction by Body System</th>
<th>Once weekly Kd 20/70 mg/m² (N = 238), n (%)</th>
<th>Twice weekly Kd 20/27 mg/m² (N = 235), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Any Grade</td>
<td>≥ Grade 3</td>
</tr>
<tr>
<td>Anemia*</td>
<td>64 (26.9)</td>
<td>42 (17.6)</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>53 (22.0)</td>
<td>26 (11.0)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>30 (12.6)</td>
<td>21 (8.8)</td>
</tr>
</tbody>
</table>
### Postmarketing Experience

The following additional adverse reactions were reported in the postmarketing experience with Kyprolis. 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: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

#### USE IN SPECIFIC POPULATIONS

**Pregnancy**

Risk Summary

Kyprolis can cause fetal harm based on findings from animal studies and the drug’s mechanism of action. There are no studies with the use of Kyprolis in pregnant women to inform drug-associated risks of adverse developmental outcomes. Kyprolis caused embryo-fetal lethality in rabbits at doses lower than the clinical dose. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Lactation

Risk Summary

There are no data on the presence of Kyprolis in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from Kyprolis is unknown, advise nursing women not to breastfeed during treatment with Kyprolis and for 2 weeks after treatment.

**Females and Males of Reproductive Potential**

Based on its mechanism of action and findings in animals, Kyprolis can cause fetal harm when administered to a pregnant woman.

**Pregnancy Testing**

Conduct pregnancy testing on females of reproductive potential prior to initiating Kyprolis treatment.

**Contraception**

- **Females**
  - Advise females of reproductive potential to avoid pregnancy and use effective contraception during treatment with Kyprolis and for at least 6 months following the final dose.
  - Advise males with female sexual partners of reproductive potential to use effective contraception during treatment with Kyprolis and for at least 3 months following the final dose.

- **Infertility**
  - Based on the mechanism of action, Kyprolis may have an effect on either male or female fertility. There are no data on the effect of Kyprolis on human fertility.

**Pediatric Use**

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

**Geriatric Use**

Of 1691 patients in clinical studies of Kyprolis, 50.4% were 65 or over, while 15.4% were 75 and over. The incidence of serious adverse events in patients 65 and over was higher than the incidence in younger patients. No overall differences in effectiveness were observed between older and younger patients.

**Hepatic Impairment**

Reduce the dose of Kyprolis by 25% in patients with mild (total bilirubin 1 to 1.5 × ULN and any AST or total bilirubin < ULN and AST < ULN) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. Dosing recommendation cannot be made for patients with severe hepatic dysfunction.

The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22.25% or 63%) than in patients with normal hepatic function (3/17 or 27%).

**Overdosage**

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for Kyprolis overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.kyprolis.com or contact Amgen Medical Information at 1-800-772-6436.

This Brief Summary is based on the Kyprolis Prescribing Information v19, 09/18. U.S. Patent Numbers: http://pat.amgen.com/kyprolis

---

### Table: Kyprolis Adverse Reactions

<table>
<thead>
<tr>
<th>Body System</th>
<th>Common</th>
<th>Infrequent</th>
<th>Very Infrequent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44 (18.5)</td>
<td>2 (0.8)</td>
<td>47 (20.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (14.3)</td>
<td>1 (0.4)</td>
<td>26 (11.1)</td>
</tr>
</tbody>
</table>

| **General Disorders and Administration Site Conditions** |        |            |                 |
| Pyrexia     | 55 (23.1) | 2 (0.8)    | 38 (16.2) | 4 (1.7) |
| Fatigue     | 48 (20.2) | 11 (4.6)   | 47 (20.0) | 5 (2.1) |
| Aedema      | 24 (10.1) | 3 (1.3)    | 25 (10.6) | 2 (0.9) |
| Peripheral edema | 18 (7.6) | 0 (0.0)    | 25 (10.6) | 2 (0.9) |

| **Infections and Infestations** |        |            |                 |
| Respiratory tract infection | 70 (29.4) | 7 (2.9)    | 79 (33.6) | 7 (3.0) |
| Pneumonia | 28 (11.8) | 24 (10.1) | 20 (8.5) | 16 (6.8) |
| Bronchitis | 27 (11.3) | 2 (0.8)    | 25 (10.6) | 5 (2.1) |

| **Musculoskeletal and Connective Tissue Disorders** |        |            |                 |
| Back pain | 28 (11.8) | 2 (0.8)    | 28 (11.9) | 4 (1.7) |

| **Nervous System Disorders** |        |            |                 |
| Headache | 25 (10.9) | 1 (0.4)    | 23 (9.8) | 1 (0.4) |

| **Psychiatric Disorders** |        |            |                 |
| Insomnia | 35 (14.7) | 2 (0.8)    | 47 (20.0) | 0 (0.0) |

| **Respiratory, Thoracic and Mediastinal Disorders** |        |            |                 |
| Cough | 37 (15.5) | 2 (0.8)    | 31 (13.2) | 0 (0.0) |
| Dyspnea | 28 (11.8) | 1 (0.4)    | 26 (11.1) | 2 (0.9) |

| **Vascular Disorders** |        |            |                 |
| Hypertension | 51 (21.4) | 13 (5.5)  | 48 (20.4) | 12 (5.1) |

Kd = Kyprolis and dexamethasone.

- Anemia includes anemia, hematocrit decreased, and hemoglobin decreased.
- Thrombocytopenia includes platelet count decreased and thrombocytopenia.
- Neutropenia includes neutrophil count decreased and neutropenia.
- Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cough includes cough and productive cough.
- Dyspnea includes dyspnea and dyspnea exertional.
- Hypertension includes hypertension and hypertensive crisis.

**Adverse Reactions Occurring at a Frequency of < 10%**

- **Blood and lymphatic system disorders**: febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombotic microangiopathy.
- **Cardiac disorders**: atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, palpitations, paracardial effusion, tachycardia.
- **Ear and labyrinth disorders**: tinnitus.
- **Eye disorders**: cataract, vision blurred.
- **Gastrointestinal disorders**: abdominal pain, abdominal pain upper, constipation, dyspepsia, toothache, vomiting.
- **General disorders and administration site conditions**: chest pain, chills, influenza like illness, infusion site reactions (including inflammation, pain, and erythema), malaise, pain.
- **Hepatobiliary disorders**: cholestasis, hepatic failure, hyperbilirubinemia.
- **Infections and infestations**: coccidioidomycosis, candidiasis, pneumocystis, toxoplasmosis, urticaria, viral infections, varicella zoster, varicella zoster skin infection.
- **Metabolism and nutrition disorders**: decreased appetite, dehydration, hypercalcinemia, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hypoproteinemia, hypophosphatemia, tumor lysis syndrome.
- **Musculoskeletal and connective tissue disorders**: muscle spasms, muscular weakness, musculoskeletal chest pain, musculoskeletal chest pain, myalgia.
- **Nervous system disorders**: cerebrovascular accident, dizziness, paresthesia, peripheral neuropathy.
- **Psychiatric disorders**: anxiety, delirium.
- **Renal and urinary disorders**: acute kidney injury, renal failure, renal impairment.
- **Respiratory, thoracic and mediastinal disorders**: acute respiratory distress syndrome, dyspnea, epistaxis, interstitial lung disease, oropharyngeal pain, pneumonitis, pulmonary hemorrhage, pulmonary embolism, pulmonary hypertension, pulmonary edema, wheezing.
- **Skin and subcutaneous tissue disorders**: erythema, hyperhidrosis, pruritus, rash.
- **Vascular disorders**: deep vein thrombosis, flushing, hypotension.

---
SITC Introduces Guidelines for Anti–PD-1 Therapy in HNSCC

by RACHEL NAROZNIAK, MA

**GUIDELINE UPDATES**

**HEAD & NECK**

**TABLE. SITC’S IMMUNOTHERAPY RECOMMENDATIONS FOR RM HNSCC: KEY HIGHLIGHTS**

<table>
<thead>
<tr>
<th>Clinical Topic</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy with PD-1 inhibitors in RM HNSCC</td>
<td><strong>First line:</strong> pembrolizumab monotherapy in treatment-naive patients and PD-L1 CPS ≥1 or pembrolizumab with chemotherapy (platinum and FU) in treatment-naive patients with biomarker-unspecified disease <strong>Second line:</strong> pembrolizumab or nivolumab monotherapy for platinum-refractory patients</td>
</tr>
<tr>
<td>Biomarker testing</td>
<td>Standard MSI testing is discouraged unless large-panel NGS is used. Positivity for PD-L1 ≥1% TPS or ≥1 CPS by IHC staining. Best use of biomarker testing is by CPS.</td>
</tr>
<tr>
<td>HPV status and use of immunotherapy</td>
<td>HPV status should not influence use of SOC immunotherapy in patients with RM HNSCC.</td>
</tr>
<tr>
<td>Role of immunotherapy in rare HNSCC subtypes</td>
<td>Prescribe cemiplimab for patients with metastatic or locally advanced cSCC in head and neck region not eligible for curative surgery or radiation. <strong>Recognize patients with NPC as distinct from patients with HNSCC. Recommend trial for patients with RM disease. Give patients with platinum-refractory NPC a PD-1/PD-L1 inhibitor if no trial is available.</strong></td>
</tr>
<tr>
<td>Patients with HNSCC who should not receive immunotherapy</td>
<td>Do not disqualify based on age, lung metastases, comorbidities, or autoimmune diseases. ICI treatment is generally suitable for patients with controlled diseases and normal CD4+ T-cell counts who are on antiretroviral therapy.</td>
</tr>
<tr>
<td>Using immunotherapy with a novel combination systemic therapy in HNSCC</td>
<td>Administer combination therapy (chemotherapy + IO) for rapidly growing disease.</td>
</tr>
</tbody>
</table>

*Similar to what we’re seeing in other solid tumor groups, the incorporation of immunotherapy has now become commonplace in head and neck cancer and at a rapid pace,* Patel said. “There needs to be a set of guidelines to help community and academic physicians treat patients as we use immunotherapy in the first line and address disease progression.”

Surgical resection of the primary tumor and lymph node draining, followed by adjuvant radiation, with or without platinum-based chemotherapy, or primary definitive concurrent chemoradiation remain the principal treatments for locally advanced HNSCC.

**CATEGORY 1 EVIDENCE FOR ANTI–PD-1**

The SITC guideline-drafting subcommittee noted that category 1 evidence exists for using single-agent anti–PD-1 immunotherapy in patients with RM HNSCC whose disease progressed after platinum-based chemotherapy or who have not received prior treatment with platinum-based chemotherapy. These data principally derive from KEYNOTE-040, KEYNOTE-012, CheckMate 141, and KEYNOTE-048.

Data from the phase Ib KEYNOTE-012 study (NCT01848834) led to the approval of pembrolizumab monotherapy in patients with RM HNSCC after the agent demonstrated tolerability and clinically meaningful antitumor activity.2 Overall survival (OS) was 13 months (95% CI, 5–not reached) and duration of response was approximately 53 weeks (12.2 months).

Moreover, 18% and 21% of patients achieved an overall response by central review and investigator assessment, respectively. Investigators said KEYNOTE-012 was the first study to**
demonstrate the effectiveness of immunotherapy for RM HNSCC.

The phase III CheckMate-141 trial (NCT02105636) precipitated the approval of nivolumab. Investigators enrolled 361 patients with recurrent HNSCC whose disease had progressed within 6 months after platinum-based chemotherapy and randomized them 2:1 to receive nivolumab every 2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab [Erbitux]).

Median OS was superior with nivolumab at 7.5 months (95% CI, 5.5-9.1) versus 5.1 months (95% CI, 4.0-6.0) with standard therapy. OS was also longer with nivolumab than with standard therapy (HR, 0.70; 97.73% CI, 0.51-0.96; P = .01).

The phase III KEYNOTE-048 trial (NCT02358031), which led to the FDA’s 2019 approvals of pembrolizumab plus chemotherapy as a frontline combination and pembrolizumab as a single agent, evaluated the efficacy of pembrolizumab alone and in combination in 882 treatment-naïve patients with locally incurable RM HNSCC.

Pembrolizumab plus chemotherapy versus cetuximab plus chemotherapy significantly improved median OS in the CPS ≥20 population (14.7 vs 11.0 months; HR, 0.60; 97.73% CI, 0.51-0.96; P = .0004) and in the CPS ≥1 population (13.6 vs 10.4 months; HR, 0.65; P < .0001).

BIOMARKER TESTING

The FDA did not require biomarker testing for use of nivolumab and pembrolizumab in patients with RM HNSCC who have progressed on or after platinum therapy. However, most patients will progress on these agents; therefore, patient selection tools are critical, the SITC guidelines note. PD-1 expression, tumor mutational burden, and immune gene signatures have been evaluated as biomarkers in HNSCC.

KEYNOTE-048 provided level 1 evidence for the use of PD-L1 expression analysis, according to the subcommittee. The approval of pembrolizumab for tumors that express PD-L1 CPS ≥1 was the first mandated biomarker testing for patients with RM HNSCC tumors. SITC said unacceptable or metastatic microsatellite instability (MSI)-high HNSCC tumors are relatively infrequent (1%-3%), which led the subcommittee (88%) to not recommend routine MSI testing.

Defining when biomarker testing is necessary and in what settings was considered of critical importance in developing the HNSCC guidelines, said Robert L. Ferris, MD, PhD, chair of the SITC Cancer Immunotherapy Guidelines Head and Neck Cancers Subcommittee.

He noted that prior authorization for biomarker testing should be added to the checklist for oncologists working with these drugs. “Testing can get confusing between lung and head cancers and neck and melanoma cancers, so it’s important for that community oncologist who may treat several diseases to remember when they’re going to need to do biomarker testing in order to get payer approval to support the use of these agents,” he said. Ferris was the co-principal investigator and lead author of CheckMate 141.

MONITORING AND EVALUATION

The SITC guidelines call for vigilant patient monitoring, evaluation, and management when using immunotherapies and note that responses to immunotherapy are vastly different than for cytotoxic chemotherapy: “Patients receiving checkpoint inhibitors may have stable disease for many months before experiencing a radiographic objective response.”

There is no level 1 evidence supporting the use of Response Evaluation Criteria in Solid Tumors (RECIST) in RM HNSCC, but all studies demonstrating efficacy of anti-PD-1 in HNSCC have used RECIST v1.1, the guidelines noted. They said such monitoring is essential during and after immunotherapy treatment. For patients experiencing a near complete response (CR) or CR following immunotherapy treatment, 53% of the subcommittee recommended continuing treatment for ≥2 years or until progression/toxicity.

The subcommittee unanimously agreed that the use of overall response rate (ORR) and overall survival (OS) to describe study outcomes post checkpoint blockade in patients with HNSCC is sufficient for future therapeutic consideration, and 41% of the subcommittee said they would favor OS over ORR. Further, 88% agreed it is not acceptable to treat patients beyond progression if there is symptomatic progression or clinical deterioration.

ELIGIBILITY FOR IMMUNOTHERAPY

Most subcommittee members indicated that their decision to recommend immunotherapy would be influenced by the presence of RM disease (89%), previous platinum therapy (78%), and patient performance status (56%).

The subcommittee agreed (81%) that autoimmune disease should not automatically exclude patients from immunotherapy but said that the specific disease should be factored into the decision whether to treat. It agreed that age (89%), lung metastases (89%), and comorbidities (75%) are not reasons for disqualifying treatment with anti–PD-1 therapy. Older patients find immunotherapies more tolerable than cytotoxic therapies, they noted.

The subcommittee also noted the value of multiple-drug regimens for increasing patient response and combating immune resistance. “As no combination strategies are currently approved in the [immunotherapy] refractory disease setting,…the subcommittee (94%) recommends enrolling a patient with RM HNSCC into a clinical trial.”

Testing can get confusing between lung and head cancers and neck and melanoma cancers, so it’s important for that community oncologist who may treat several diseases to remember when they’re going to need to do biomarker testing in order to get payer approval to support the use of these agents.”

—ROBERT L. FERRIS, MD, PHD
GUIDE LIND UPDATE

HEAD & NECK

GUIDELINE UPDATE

assessing a combination immunotherapeutic approach,” they wrote.

For locally recurrent disease, which carries no option for surgical or radiation therapy, and for metastatic disease in the first-line setting, the standard of care remains platinum-based doublet chemotherapy with cetuximab. Until recently, second-line treatments were limited to cetuximab, methotrexate, and a taxane before the 2016 and 2019 immunotherapeutic gains. Each agent generates response rates of 10% to 13% and a median progression-free survival of 2 to 3 months. None is associated with a clear improvement in OS.

SITC began writing the HNSCC guidelines in 2018, delaying publication to ensure that the recommendations reflected findings from KEYNOTE-048 and the anticipated pembrolizumab approval. “When the positive data from this trial were presented at the 2018 [European Society for Medical Oncology] congress, we knew we’d eventually have not only approvals for the second line but [also] an imminent approval in the first line,” Ferris said.

“We knew the FDA had to issue a decision on pembrolizumab in HNSCC by its action date of June 10, 2019,” Ferris said. “It was all quite well timed.”

HNSCC is the ninth leading cancer by incidence worldwide and constitutes 90% of all head and neck cancers.1 The cancer develops in the squamous mucosal lining of the upper aerodigestive tract, including the lip, oral, and nasal cavities and the paranasal sinuses, nasopharynx, oropharynx, larynx, and hypopharynx, and accounts for more than 10,000 deaths in the United States each year. The majority of diagnoses are for locally advanced disease that carries a high risk of recurrence. In contrast, about 10% of cases are metastatic at diagnosis.

NCCN Grants Category 1 Recommendation to Pexidartinib for TGCT by GINA COLUMBUS

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) has updated its Clinical Practice Guidelines in Oncology for Soft Tissue Sarcoma to include a category 1 recommendation for pexidartinib (Turalio) for the treatment of patients with tenosynovial giant cell tumor (TGCT).1

The recommendation is based on findings from the placebo-controlled phase III ENLIVEN trial (NCT02371369), which was also the basis for pexidartinib’s August 2019 FDA approval for the treatment of adult patients with symptomatic TGCT that is associated with severe morbidity or functional limitations and not responsive to improvement with surgery. Results of ENLIVEN demonstrated that pexidartinib elicited a 39% overall response rate (ORR; 95% CI, 27%-53%) with pexidartinib compared with 0% (95% CI, 0%-6%; P < .0001) with placebo following 25 weeks of treatment based on central review of MRI scans.2

A category 1 recommendation means that based upon high level of evidence, there is uniform consensus that the intervention is appropriate. The NCCN also recommends imatinib (Gleevec) as a systemic therapy for patients with TGCT.1

TGCT, which is also known as pigmented villonodular synovitis or giant cell tumor of the tendon sheath, is a nonmalignant tumor of the joint or tendon sheath. The disease can be locally aggressive and debilitating and is associated with severe morbidity or function limitations. The multicenter, double-blind, ENLIVEN study (NCT02371369) had 2 parts, the first of which was a double-blind phase. In this phase, 120 patients with symptomatic advanced TGCT—in whom surgical removal of the tumor would lead to potentially worsening functional limitation or severe morbidity—were randomized 1:1 to receive either pexidartinib (n = 61) or placebo (n = 59) at 1000 mg daily for 2 weeks followed by 800 mg daily for 22 weeks.

Patients who were eligible for enrollment had historically confirmed, advanced, symptomatic TGCT with measurable disease ≥2 cm by RECIST v1.1 criteria. Patients were also stratified by US or non-US sites, as well as upper versus lower extremity. Fifty-nine percent of patients were female, and 88% of patients overall were Caucasian. The median age was 45 years (range, 18-79), 8% of patients had upper extremity involvement, and the remaining 92% had lower extremity involvement.

The primary end point was percentage of patients achieving a complete or partial response (PR), assessed with centrally read MRI scans using RECIST 1.1 criteria, following 24 weeks of treatment. Secondary end points included ROM, response by tumor volume score (TVS), Patient-Reported Outcomes Measurement Information System (PROMIS) physical function, stiffness, and measures of pain reduction.

Findings demonstrated that the complete response rate of 15% and a PR rate of 23%. The median duration of response (DOR) was not reached with pexidartinib (range, 4.6+ to 24.9+) and was not available with placebo. Ninety-six percent of patients had a DOR ≥6 months, and 50% of patients had a DOR ≥12 months. At a median 6 months of follow-up, none of the responders in the trial progressed. Tumor response was assessed by TVS, which was 56% (95% CI, 43.3%-67.5%) with pexidartinib and 0% (95% CI, 0%-6.1%) with placebo (P < .0001). The responses also correlated with improved patient symptoms and function.

The prescribing information for pexidartinib includes a Boxed Warning to inform the risk of serious and potentially fatal liver injury. Liver tests should be monitored prior to start of treatment and at specified intervals during therapy. Should liver tests become abnormal, pexidartinib may need to be withheld, the dose reduced, or be permanently discontinued, depending on the severity of the liver injury. The agent is only available through the Risk Evaluation and Mitigation Strategy Program.

REFERENCES


WE’RE 1 OF ONLY 16 CANCER CENTER CONSORTIA IN THE U.S. APPROVED BY THE NATIONAL CANCER INSTITUTE

John Theurer Cancer Center is now a consortium member of the NCI-designated Georgetown Lombardi Comprehensive Cancer Center. Working together, our patients will have greater access to innovative clinical trials, which will help turn discovery into cures faster. John Theurer Cancer Center at Hackensack University Medical Center – we’re not just at the forefront of cancer, we’re pioneering the possible.

Hackensack Meridian Health
John Theurer Cancer Center

Consortium Member of

Georgetown | Lombardi COMPREHENSIVE CANCER CENTER

Learn more, visit JTCancerCenter.org.
IDO Inhibitor Development Shows Fresh Signs of Life

By JANE DE LARTIGUE, PHD

IN THE ONGOING SEARCH for novel immunotherapies that might rival or surpass the efficacy of immune checkpoint inhibitors (ICIs), drugs targeting IDO1—a key enzyme in tryptophan metabolism—have been a major focus in recent years.

Lead candidate epacadostat seemed to offer significant potential in combination with the PD-1-targeting ICI pembrolizumab (Keytruda), and Incyte Corporation advanced the regimen rapidly into phase III clinical trials. 

Other pharmaceutical companies also were diving into the field. Another immunotherapy success story appeared imminent until the failure of the ECHO-301 trial testing the combination of epacadostat and pembrolizumab2 sent shockwaves through the field. Following these negative results, Incyte took a sledgehammer to its IDO inhibitor program, halting enrollment across a swathe of ongoing pivotal trials.3 The anxiety spread. Bristol-Myers Squibb undertook a complete overhaul of its IDO inhibitor program,4,6 and it was the final nail in the coffin for a tentative IDO collaboration between Genentech and NewLink Genetics, an alliance that had suffered setbacks of its own in recent years.7,8

The ECHO-301 trial may serve as a cautionary tale against rushing into inadequately planned clinical testing of an agent with limited and suboptimal preclinical data. Some investigators have argued that these caveats should be considered “when weighing the implications of this one trial against the overall potential” of agents that inhibit IDO and TDO, another tryptophan-catabolizing enzyme. The rapid pace of clinical development may have come at the cost of a thorough understanding of this highly complex pathway and its nuanced role in cancer development.9 These difficulties, however, have not deterred new entrants into the field. Several companies are developing IDO1 inhibitors with a novel mechanism of action.10-12 Dual inhibitors of IDO1 and TDO are also being developed to address functional redundancy between these enzymes, a potential mechanism of resistance to IDO1 inhibition. Other studies are exploring alternative ways of targeting the broader pathway of tryptophan metabolism that IDO1 regulates.9

These efforts suggest that the IDO pathway story is far from over.

LEVERAGING AN ESSENTIAL AMINO ACID
Tryptophan is the rarest of the essential amino acids—those that must be acquired through the diet—and, as such, its metabolism is tightly regulated.13 Several biochemical pathways are involved in tryptophan breakdown, but the kynurenine (KYN) pathway predominates, converting tryptophan into biologically active metabolites, including the eponymous KYN.13-17

The rate-limiting step in this pathway involves several heme-containing metalloenzymes: IDO1, or indoleamine 2,3-dioxygenase 1; the closely related IDO2; and TDO, or tryptophan 2,3-dioxygenase. All 3 enzymes catalyze the same reaction, but in different tissue types. TDO is most highly expressed in the liver and is the major mediator of hepatic tryptophan metabolism. IDO1 has a broader range of expression than TDO and IDO2 and recognizes other indole-containing substrates besides tryptophan. IDO2 also is much less well studied than the other enzymes.13-18

IDO and TDO expression is regulated by a range of nutritional and inflammatory signals. TDO can be activated by tryptophan, cholesterol, prostaglandin E2, and others, while regulators of IDO activity include interferon gamma, interleukin 6, and tumor necrosis factor alpha.13-17

IDO-mediated tryptophan depletion has 3 major downstream effects. First, it activates general control nonrepressible 2 (GCN2), a serine/threonine kinase that senses amino acid deficiency and phosphorylates eukaryotic translation initiation factor 2 alpha, leading to reduced protein production and inducing apoptosis of effector T (Teff) cells.13-17

Second, IDO-mediated tryptophan metabolism inhibits a master regulator of metabolism, mTOR, which feeds into a network of amino acid sensors, indicating to the cell that the available supply of tryptophan is low. Third and last, it activates the aryl hydrocarbon receptor (AhR), a transcription factor that controls the function of a plethora of immune cells. Adding to the complexity, AhR itself can activate IDO1, both directly and indirectly, establishing a positive regulatory feedback loop13-17 (FIGURE17).

IDO’S IMMUNOSUPPRESSIVE ROLE
Increased tryptophan metabolism in advanced
cancers was first noted in the 1950s, but this remained a relatively obscure observation until IDO was linked to immunosuppression, suggesting that cancer cells were hijacking this immunosuppressive activity to evade immune detection.

IDO1 overexpression has now been observed across many tumor types. It has been found to be under the control of BIN1, a tumor suppressor protein that is commonly attenuated in cancer, revealing one of the mechanisms of increased IDO1 expression in tumors.

Moreover, IDO1 is expressed not only by cancer cells but also by stromal, endothelial, and immune cells of the tumor microenvironment. IDO2 and TDO have also been shown to be overexpressed in some cancers, and IDO1 and TDO may be co-expressed in a substantial proportion of tumors.

IDO1 expression has varied effects on different immune cells, including blocking the activation of Teff cells, stimulating the activation of regulatory T cells, and inhibiting natural killer cell function, in addition to promoting the differentiation of tolerogenic dendritic cells and the activation and expansion of myeloid-derived suppressor cells. Collectively, this fosters a highly immunosuppressive local environment.

The first downstream mediator of this immunosuppressive role to be identified was activation of GCN2, but the importance of the AhR and mTOR pathways has also come to light more recently. The jury is still out on which pathway is most important in this regard, and it may be that effector pathways have different degrees of importance in different tumor types.

**DEVELOPMENT RAMPS UP**

Indoximod became the first IDO inhibitor to undergo clinical testing. In a phase II study in 135 patients with metastatic pancreatic cancer, indoximod was combined with gemcitabine and nab-paclitaxel (Abraxane). Among 104 patients evaluable for efficacy, the overall response rate (ORR) was 46.2%, with a complete response (CR) rate of 1.0% and a partial response (PR) rate of 45.2%. The combination was well tolerated. Median overall survival was 10.9 months, but the study did not meet its prespecified goal of a 30% reduction in hazard ratio.

A separate phase II trial of indoximod in combination with taxane chemotherapy (docetaxel or paclitaxel) also failed to meet its primary endpoint of statistically significant improvement in progression-free survival (PFS) in patients with metastatic breast cancer.

Several bona fide direct catalytic inhibitors of IDO1 have been developed. The lead candidate, epacadostat, competes with tryptophan 2,3-dioxygenase (IDO).**TABLE. IDO INHIBITORS IN CLINICAL DEVELOPMENT**

<table>
<thead>
<tr>
<th>Trial Description (ClinicalTrials.gov identifier)</th>
<th>Estimated Enrollment</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epacadostat (Incyte)²⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ pembrolizumab and tavokinogene telseplasmid (gene therapy) in HNSCC (NCT03823131)</td>
<td>34</td>
<td>II</td>
</tr>
<tr>
<td>+ pembrolizumab and CRS-207 (immunotherapy cancer vaccine) +/- CY/GVAX pancreas vaccine in metastatic pancreatic cancer (NCT03006302)</td>
<td>70</td>
<td>II</td>
</tr>
<tr>
<td>+ preoperative CRT in locally advanced rectal cancer (NCT03516708)</td>
<td>39</td>
<td>I</td>
</tr>
<tr>
<td>+ GM-CSF vaccine (SV-BR-1-GM) and INCMGA00012 (PD-1 inhibitor) in breast cancer (NCT03328026)</td>
<td>60</td>
<td>I/II</td>
</tr>
<tr>
<td>+ avelumab (anti-PD-L1 mAb), bevacizumab (anti-VEGF mAb), and RT in recurrent glioma (NCT03532295)</td>
<td>55</td>
<td>I/II</td>
</tr>
<tr>
<td>+ SD-101 (toll-like receptor 9 agonist) and RT in advanced solid tumors and lymphomas (UCD-CC#271/NCT03322384)</td>
<td>56</td>
<td>I/II</td>
</tr>
<tr>
<td>Indoximod (NewLink Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ CRT in pediatric relapsed brain tumors or newly diagnosed DIPG (NCT04049669)</td>
<td>140</td>
<td>II</td>
</tr>
<tr>
<td>+ chemotherapy in newly diagnosed AML (NCT02835729)</td>
<td>40</td>
<td>I</td>
</tr>
<tr>
<td>+ temozolomide (chemotherapy/alkylating agent) in progressive pediatric brain tumors (NCT02502708)</td>
<td>115</td>
<td>I</td>
</tr>
<tr>
<td>Linrodostat (BMS-986205; Bristol-Myers Squibb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ chemotherapy +/- nivolumab in muscle-invasive bladder cancer (NCT03661320)</td>
<td>1200</td>
<td>III</td>
</tr>
<tr>
<td>+ nivolumab in HNSCC (NCT03854032)</td>
<td>48</td>
<td>II</td>
</tr>
<tr>
<td>+ nivolumab in recurrent/resistant endometrial cancer (NCT04106414)</td>
<td>50</td>
<td>II</td>
</tr>
<tr>
<td>+ nivolumab +/- BCG (immunotherapy) in BCG-unresponsive non-muscle-invasive bladder cancer (CheckMate 9UT/NCT03519256)</td>
<td>436</td>
<td>II</td>
</tr>
<tr>
<td>+ nivolumab +/- ipilimumab as neoadjuvant therapy in resectable melanoma (NCT04007588)</td>
<td>45</td>
<td>II</td>
</tr>
<tr>
<td>+ nivolumab in advanced RCC (FRACtion-RCC/NCT02996110)</td>
<td>200</td>
<td>II</td>
</tr>
<tr>
<td>+ nivolumab in advanced gastric cancer (FRACtion-GC/NCT02935634)</td>
<td>600</td>
<td>II</td>
</tr>
<tr>
<td>+ nivolumab +/- ipilimumab in advanced cancers (NCT02658890)</td>
<td>907</td>
<td>I/II</td>
</tr>
<tr>
<td>+ nivolumab and RT +/- temozolomide in newly diagnosed glioblastoma (NCT04047706)</td>
<td>30</td>
<td>I</td>
</tr>
<tr>
<td>+ nivolumab and relatlimab (anti–LAG-3 mAb) in advanced solid tumors (NCT03459222)</td>
<td>230</td>
<td>I/II</td>
</tr>
<tr>
<td>NGL802 (NewLink Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In advanced solid tumors (NCT03164603)</td>
<td>36</td>
<td>I</td>
</tr>
<tr>
<td>HKK2455 (Kyowa Kirin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ avelumab in advanced urethelial cancer (NCT03915405)</td>
<td>44</td>
<td>I</td>
</tr>
<tr>
<td>+/- mogamulizumab (anti-CCR4 mAb) in advanced solid tumors (NCT02867007)</td>
<td>50</td>
<td>I</td>
</tr>
<tr>
<td>HTI-1090 (SHR-9146; IDO1/TDO inhibitor) (Hengrui Therapeutics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ SHR-1210 (PD-1 inhibitor) +/- apatinib (VEGFR inhibitor) in advanced solid tumors (NCT0349163)</td>
<td>44</td>
<td>I</td>
</tr>
<tr>
<td>LY3381916 (Eli Lilly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/- LY3300054 (PD-L1 inhibitor) in advanced solid tumors (NCT03343613)</td>
<td>175</td>
<td>I</td>
</tr>
<tr>
<td>PD-L1/IDO peptide vaccine (Herlev Hospital/IO Biotech)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ nivolumab in metastatic melanoma (NCT03047928)</td>
<td>50</td>
<td>I/II</td>
</tr>
</tbody>
</table>

A separate phase II trial of indoximod in combination with taxane chemotherapy (docetaxel or paclitaxel) also failed to meet its primary endpoint of statistically significant improvement in progression-free survival (PFS) in patients with metastatic breast cancer.

Several bona fide direct catalytic inhibitors of IDO1 have been developed. The lead candidate, epacadostat, competes with tryptophan 2,3-dioxygenase (IDO).
tryptophan for binding to the IDO1 catalytic site. In concert with Genentech, NewLink Genetics developed navoximod, a tryptophan noncompetitive inhibitor that is also a weak inhibitor of TDO.16-23

Bristol-Myers Squibb and Pfizer also threw their hats into the ring with the development of linrodoostat (BMS-986205) and PF-06840003, respectively.24,25

Clinical trials of epacadostat monotherapy were disappointing, with no objective responses.26-28 Studies suggesting that IDO1 overexpression may serve as a mechanism of resistance to ICIs, targeting PD-1 and its ligand PD-L1 and demonstrating synergy between the two types of therapy, served as the rationale for pursuing clinical trials of this combination, which initially showed great promise.16

PROMISING DOUBLE ACT?
Enthusiasm for combining IDO inhibitors with ICIs began building after findings from a study of indoximod plus investigator’s choice of nivolumab (Opdivo), pembrolizumab, or ipilimumab (Yervoy) in patients with advanced melanoma produced an ORR of 55.7% and a CR rate of 18.6%.10

In the ECHO-202 study, epacadostat combined with pembrolizumab showed efficacy across several tumor types in patients with advanced cancers. Among 62 patients, the ORR was 40.3%, including 8 CRs and 17 PRs. Patients with melanoma had an ORR of 55%, and responses were also seen in patients with non–small cell lung cancer (NSCLC), renal cell carcinoma, endometrial adenocarcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma (HNSCC).1

The combination of navoximod plus atezolizumab (Tecentriq) elicited PRs in 9% of patients and stable disease in a further 17% in a phase I clinical trial.29 In a phase I/II trial of linrodoostat in combination with nivolumab, among 27 patients with immunotherapy-naïve advanced bladder cancer, the ORR was 37%, including 3 CRs and 7 PRs.30

On the basis of these promising data, numerous IDO inhibitor–ICI combinations advanced to phase III clinical trials. The future looked rosy until Incyte reported the findings from the ECHO-301 trial, which evaluated the combination of epacadostat and pembrolizumab.

A total of 706 patients with advanced melanoma were randomly assigned to receive either the combination or pembrolizumab plus placebo. Over a median follow-up of 12.4 months, across all prespecified and post hoc subgroups examined, there was no significant difference in PFS between the 2 groups (median PFS, 4.7 months vs 4.9 months, respectively). An independent data monitoring committee recommended that the study be stopped, and no additional efficacy analyses are planned at this time.2

The failure stunned the research community and threw up a large roadblock to IDO inhibitor development. It prompted Incyte to halt enrollment in ongoing pivotal trials of epacadostat paired with pembrolizumab, nivolumab, or durvalumab (Imfinzi).3 Bristol-Myers Squibb followed suit and suspended trials of linrodoostat in NSCLC and HNSCC.4

NewLink Genetics halted the randomization portion of Indigo301, a phase I/II study involving combinations of indoximod with nivolumab or pembrolizumab in advanced melanoma.14 The company also shifted the focus for indoximod away from melanoma to 3 other indications: recurrent pediatric brain tumors, diffuse intrinsic pontine glioma, and acute myeloid leukemia (AML).5,6

The ECHO-301 failure was also the final straw for the collaboration between NewLink Genetics and Genentech, which was terminated in May 2018.7

MOVING FORWARD
Despite the domino effect triggered by ECHO-301 and other clinical trial failures, enthusiasm for IDO inhibitors has not been completely extinguished. At least 8 agents are under study in ongoing clinical trials, including select studies into epacadostat and indoximod that are still recruiting (TABLE).

New data from initial indoximod studies in brain tumors and AML have been promising. Among 29 pediatric patients with advanced brain tumors enrolled in an ongoing phase I clinical trial of indoximod combined with chemotherapy and radiation therapy, the median PFS was 6.2 months, and 9 patients were continuing treatment at the time of data presentation.8

In an ongoing phase I trial, among 25 patients with newly diagnosed AML treated with indoximod and induction chemotherapy who received at least 1 dose of indoximod, 84% achieved remission, and the rate of minimal residual disease-negative status was promising at 83%.9

NewLink Genetics is developing a prodrug of indoximod, NLG802, and early clinical trial results were presented in May at the Immuno-Oncology World Congress in Barcelona, Spain. NLG802 exhibited a tolerable safety profile with no dose-limiting toxicities in findings from a phase I study in 26 patients with recurrent advanced solid tumors refractory to chemotherapy or targeted agents.10

Meanwhile, Bristol-Myers Squibb is pursuing linrodoostat across a range of tumor types in multiple clinical trials. These include a phase III trial that seeks to recruit 1200 patients with non–muscle-invasive bladder cancer. The study is testing neoadjuvant gemcitabine, cisplatin, and nivolumab with or without linrodoostat, followed by nivolumab with or without linrodoostat versus chemotherapy after radical cystectomy (NCT03661320).

Linrodoostat is being evaluated in combination with nivolumab and nivolumab plus ipilimumab in an estimated 907 patients with advanced cancers, including melanoma and NSCLC (NCT02658890).

New entrants also are entering the field. Kyowa Hakko Kirin, a Japanese company, and Eli Lilly are both developing IDO inhibitors with a novel mechanism of action. Since many conventional IDO inhibitors have structural similarity to tryptophan, they can activate AhR downstream of IDO. This can trigger the positive feedback activation of IDO, potentially confounding the effects of IDO inhibition.11 The new IDO inhibitors target the apo form of IDO1, which lacks heme, and reportedly avoid inadvertent AhR agonism.12-14

Additionally, several pharmaceutical companies are exploring more potent dual IDO/TDO inhibitors, with HTI-1090 the first to enter clinical trials.

Finally, if AhR is the most important downstream effector in regard to IDO’s role in cancer immunosuppression, as some investigators suspect, then inhibiting this protein could also have significant anticancer efficacy.15 An AhR-inhibiting agent, BAY2416964, recently entered first-in-human clinical testing in patients with advanced solid tumors (NCT04069026).
XPOVIO™ (selinexor) 20 mg tablet

NOW APPROVED

For relapsed or refractory multiple myeloma
The first and only approved oral nuclear export inhibitor that blocks XPO1

Learn more about this novel treatment approach at XPOVIO.com

INDICATION

XPOVIO is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

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

Please see additional Important Safety Information continued on the following page and XPOVIO Full Prescribing Information on XPOVIO.com.
Thrombocytopenia
XPOVIO can cause thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia occurred in 61% of patients treated with XPOVIO. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia and fatal hemorrhage occurred in <1% of patients.

Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia
XPOVIO can cause neutropenia, potentially increasing the risk of infection. Neutropenia was reported as an adverse reaction in 34% of patients, and severe (Grade 3-4) neutropenia occurred in 21% of patients treated with XPOVIO. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients.

Obtain neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity
Gastrointestinal toxicities occurred in patients treated with XPOVIO.

Nausea/Vomiting
Nausea was reported as an adverse reaction in 72% of patients, and Grade 3 nausea occurred in 9% of patients treated with XPOVIO. The median time to onset of the first nausea event was 3 days.

Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients treated with XPOVIO. The median time to onset of the first vomiting event was 5 days.

Provide prophylactic 5-HT3 antagonists and/or other anti-nausea agents, prior to and during treatment with XPOVIO. Manage nausea/vomiting by dose interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated.

Diarrhea
Diarrhea was reported as an adverse reaction in 44% of patients, and Grade 3 diarrhea occurred in 6% of patients treated with XPOVIO. The median time to onset of diarrhea was 15 days.

Manage diarrhea by dose modifications and/or standard anti-diarrheal agents; administer intravenous fluids to prevent dehydration in patients at risk.

Anorexia/Weight Loss
Anorexia was reported as an adverse reaction in 53% of patients, and Grade 3 anorexia occurred in 5% of patients treated with XPOVIO. The median time to onset of anorexia was 8 days.

Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with XPOVIO. The median time to onset of weight loss was 15 days.

Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dose modifications, appetite stimulants, and nutritional support.

Please see additional Important Safety Information continued on the following page and XPOVIO Full Prescribing Information on XPOVIO.com.
**IMPORTANT SAFETY INFORMATION (cont’d)**

**Hyponatremia**
XPOVIO can cause hyponatremia; 39% of patients treated with XPOVIO experienced hyponatremia, 22% of patients experienced Grade 3 or 4 hyponatremia. The median time to onset of the first event was 8 days.

Monitor sodium level at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Treat hyponatremia per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

**Infections**
In patients receiving XPOVIO, 52% of patients experienced any grade of infection. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. Grade ≥3 infections were reported in 25% of patients, and deaths resulting from an infection occurred in 4% of patients. The most commonly reported Grade ≥3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis. Most infections were not associated with neutropenia and were caused by non-opportunistc organisms.

**Neurological Toxicity**
Neurological toxicities occurred in patients treated with XPOVIO.

Neurological adverse reactions including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients, and severe events (Grade 3-4) occurred in 9% of patients treated with XPOVIO. Median time to the first event was 15 days.

Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerating dizziness or mental status changes.

**Embryo-Fetal Toxicity**
Based on data from animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

**ADVERSE REACTIONS**
The most common adverse reactions (incidence ≥20%) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose, and 65.3% had the dose of XPOVIO interrupted. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia. The rate of fatal adverse reactions was 8.9%.

Of the 202 patients with RRMM who received XPOVIO, 49% were 65 years of age and over, while 11% were 75 years of age and over. No overall difference in effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients. When comparing patients 75 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (44% vs 27%), higher incidence of serious adverse reactions (70% vs 58%), and higher incidence of fatal adverse reactions (17% vs 9%).

Please see XPOVIO Full Prescribing Information.

New Sequencing Approaches Shape Follicular Lymphoma Landscape

By CHRISTINA T. LOGUIDICE

FOLLICULAR LYMPHOMA (FL) IS an indolent non-Hodgkin lymphoma that often requires multiple lines of treatment after it relapses or becomes refractory to standard therapies. With a variety of available agents, including the more recently approved R² regimen of lenalidomide (Revlimid) plus rituximab (Rituxan) as well as the PI3K inhibitor duvelisib (Copiktra), determining which treatments to choose and how best to sequence them can be challenging.

During a recent OncLive Peer Exchange® program, a panel of lymphoma experts discussed their approach to selecting and sequencing FL treatments. Overall, based on the recent FDA approvals, the panelists favored using R² in the second line and PI3K inhibitors in the third line, and they discussed the differences between the PI3K inhibitors currently approved for FL.

“R² IN THE SECOND LINE

In May, the FDA approved R² for patients with previously treated FL or marginal zone lymphoma (MZL).¹ “[For] the first time, there is a chemotherapy-free regimen with an immunomodulator, lenalidomide, and an anti-CD20 monoclonal, rituximab,” Pier Luigi Zinzani, MD, PhD, said, adding later that he thinks it will become the best second-line treatment for patients with FL.

R² was approved based on 2 clinical trials, AUGMENT (NCT01938001) and MAGNIFY (NCT01996865).¹ ² AUGMENT randomly assigned 358 patients with relapsed/refractory FL (n = 295) or MZL (n = 63) to R² (n = 178) or rituximab-placebo (n = 180).² In patients with FL, the overall response rate (ORR) by independent review committee (IRC) assessment was 80.0% (118 of 147 patients; 95% CI, 73%-86%) in the R² arm versus 55.4% (82 of 148 patients; 95% CI, 47%-64%) in the placebo arm.¹

Progression-free survival (PFS) was also significantly improved in the R² arm versus the placebo arm, with an HR of 0.46 (95% CI, 0.34-0.62; P < .001) and a median duration of response (DOR) of 39.4 months (95% CI, 22.9–not reached) versus 14.1 months (95% CI, 11.4-16.7), respectively.² MAGNIFY was designed to determine the optimal duration of lenalidomide.³ It randomly assigned 370 patients with FL or MZL and stable disease or better (N = 370) who were previously treated with ≥1 prior therapy to continued R² versus rituximab maintenance.³ In those with FL, the ORR by investigator assessment was 59% (104 of 177; 95% CI, 51%-66%).³ At a median follow-up of 16.7 months, the median DOR was 36.8 months and the median PFS was 36.0 months.³

Although R² showed a good clinical response and had an acceptable safety profile, the panelists noted that some challenges with toxicity can exist. Across AUGMENT and MAGNIFY, the most common adverse events (AEs) were neutropenia, fatigue, diarrhea, constipation, nausea, and cough.³ However, lenalidomide is also associated with hematologic toxicity and venous and arterial thromboembolism, which can become life-threatening or fatal.³ The
Panelists noted that dose modifications can help mitigate these risks. “I think you have to be on guard for dose reductions and dose holds. The cytopenias are very responsive to growth factor and dosing holds, but respect those and don’t press the envelope in a disease where the goal is quality of life for as long as possible,” Matthew Lunning, DO, said.

John M. Pagel, MD, PhD, concurred, adding, “A lot of these people will do very well with great efficacy at lower doses, so I have a very low threshold to dose-reduce.” He indicated that he also often starts patients at lower doses and that he would use this regimen for patients with more aggressive disease that is likely to relapse more quickly (eg, relapse <1 year after front-line treatment). “[Although these patients] are going to end up doing worse than somebody who has longer remissions from up-front therapy, I like the idea of doing something that’s not the same type of chemotherapy/noctidose-reduce.” He indicated that he also often starts patients at lower doses and that he would use this regimen for patients with more aggressive disease that is likely to relapse more quickly (eg, relapse <1 year after front-line treatment). “[Although these patients] are going to end up doing worse than somebody who has longer remissions from up-front therapy, I like the idea of doing something that’s not the same type of chemotherapy/noctidose-reduce.”

PI3K INHIBITORS IN THE THIRD LINE

Currently, 3 PI3K inhibitors are approved to treat FL: idelalisib (Zydelig), copanlisib (Aliqopa), and, more recently, duvelisib (TABLE).

Duvelisib received accelerated approval in September 2018 for adult patients with relapsed or refractory FL after ≥2 prior systemic therapies based on data from the DYNAMO + R trial (NCT02204982). The study included 129 patients, 83 patients with FL, who were refractory to rituximab and to either chemotherapy or radioimmunotherapy.

The ORR by IRC in the FL arm was 42% (95% CI, 31%-54%). Thirty-four patients (41%) with FL had a partial response and 1 patient (1%) had a complete response.

Among these 35 responders, 15 (43%) maintained responses for ≥6 months and 6 (17%) maintained responses for ≥12 months. The estimated median DOR among all 129 patients was 10 months, and the estimated median PFS was 9.5 months. “The label is not exactly the patients who were on the trial. It’s for [patients with 2 prior therapies], not just [those with] double refractory [disease], which I think is helpful in everyday practice,” Flinn said.

The panelists discussed the challenge of determining which PI3K inhibitor to choose. They noted that each inhibitor targets different PI3K isoforms, with idelalisib targeting the δ isoforms, copanlisib targeting the δ and α isoforms, and duvelisib targeting the δ and γ isoforms.

Pagel said that although he finds duvelisib’s dual isoform action scientifically exciting, the clinical relevance of this mechanism in FL remains unclear. “The idea [is] that maybe it’s causing some changes in the tumor microenvironment that would be important for inhibiting cell growth or proliferation—so it’s through interactions with myeloid cells or even T cells in the microenvironment...[but] from a clinical translation, I’m not sure they necessarily make a difference that we’ve seen,” he said, adding that the results from ongoing T-cell studies will provide more information.

One such ongoing study is PRIMO (NCT03372057), which is assessing the safety and efficacy of duvelisib in patients with relapsed/refractory peripheral T-cell lymphoma. The panelists also agreed that it is unclear whether a benefit exists in targeting the α isoform in patients with FL. They indicated that thus far, the benefit has been shown in mantle cell lymphoma only, with no data available in FL.

Another difference between PI3K inhibitors that the panelists discussed is their administration. Although duvelisib and idelalisib are taken orally twice daily, copanlisib requires intravenous (IV) administration. “Copanlisib has been limited in its use and exposure in the United States simply because of that IV administration’s weekly for 3 weeks out of 4...that’s a lot of infusion time in the treatment center. Eventually there’s fatigue with that from a patient standpoint,” Pagel said. Subsequently, patients on a copanlisib regimen may be more likely to be placed on a drug holiday, he said.

The panelists suggested that both the isoform action and dosing schedule of the available PI3K inhibitors may affect their toxicity profiles. “The initial hypothesis with idelalisib was that by hitting the specific isoform, you would not get the off-target toxicity or the toxicity associated with hitting the other isoforms. Of course, there’s another potential corollary to that: By hitting only the δ isoform, you’re going to open yourself up to some of the immunologic toxicities that were predicted in a mouse model prior to that,” Flinn said.

Currently, copanlisib is the only approved PI3K inhibitor in FL that does not have a boxed warning, and it is generally associated with milder and more easily managed AEs, such as hyperglycemia and hypertension. In contrast, idelalisib and duvelisib...
have boxed warnings regarding a variety of serious and potentially fatal toxicities, including infections, diarrhea/colitis, skin reactions, and pneumonitis.\textsuperscript{4,6} Flinn and Zinzani suggested this difference in toxicity profile may stem from the different dosing schedules. Although copanlisib requires IV administration, it is given over 1 hour on days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule of 3 weeks on and 1 week off, unlike the daily treatment required with duvelisib and idelalisib.\textsuperscript{4,6} Consequently, alternative dosing schedules are being examined for duvelisib, such as drug holidays, decreased dosing, and induction to see whether such modifications might improve its AE profile, Flinn said.

Although no head-to-head comparisons exist to guide selection between the available PI3K inhibitors, the panelists emphasized the importance of remembering these agents in the treatment armamentarium for FL. "This class of drugs should not be forgotten in this disease. I have had patients on a PI3K inhibitor with relapsed FL who have had really quite striking turn-around of their disease and done extremely well for a long period," Pagel said.

**EMERGING TREATMENTS**

Several emerging therapies, including various immunotherapy regimens, are currently in clinical trials, have the potential to change the treatment landscape. One such agent is polatuzumab vedotin-piiq (Polivy), an anti-CD79b antibody–drug conjugate. It was studied in combination with bendamustine and rituximab in patients with either relapsed/refractory FL or diffuse large B-cell lymphoma (DLBCL).\textsuperscript{10} Although it did not show benefit in FL, it did show benefit in DLBCL, resulting in FDA approval in June 2019 as a combination regimen with bendamustine and rituximab for adult patients with relapsed/refractory DLBCL, not otherwise specified, after ≥2 prior therapies.\textsuperscript{10}

However, the panelists noted that another study that combined polatuzumab with obinutuzumab (Gazyva) and lenalidomide has shown promise in FL.\textsuperscript{11} "It was a phase I study in which they were dose-escalating the polatuzumab and the lenalidomide...and when they figured out the recommended phase II dose, it had a pretty good ORR—I think about a 50% complete remission [CR] rate," Lunning said.

Although checkpoint inhibitors have revolutionized the treatment of many solid tumors, the panelists noted that this has not necessarily been the case with lymphomas. However, they discussed a small study that appears to deviate from that trend. The study combined pembrolizumab (Keytruda) with rituximab in 27 patients with FL.\textsuperscript{12} "The CR rate was 50% in relapsed and refractory patients with FL, and the overall response rate was 65%," Zinzani said. The treatment was well tolerated, with most AEs being mild (grade ≤2).\textsuperscript{12} Grade 3 events included nausea, infusion reactions, aseptic meningitis, and pneumonia.\textsuperscript{12}

The panelists said more studies are needed before checkpoint inhibitors can be comfortably used in FL. "They can be extremely toxic and if we don’t really understand how to use them in FL, we have to be very cautious," Pagel emphasized.

CAR T-cell therapy has been a significant breakthrough in cancer treatment, showing favorable impact in patients with hematologic malignancies associated with poor outcomes; however, its role in treating an indolent disease such as FL remains unclear, the panelists noted.

"At the end of the day, there is a small subset of patients potentially eligible for CAR T-cells," Zinzani said. He suggested CAR T-cell therapy could potentially be considered as a consolidation therapy instead of autologous or allogeneic transplantation, whereas Lunning said another use may be in patients with transformed FL, which is another area of unmet medical need. More studies are needed to better delineate the role of CAR T-cell therapy.

An agent that the panelists found particularly exciting is tazemetostat, an EZH2 inhibitor. "It is the first epithelial agent that we have in follicular lymphoma," Pagel said.

In an open-label, multicenter, phase II study that enrolled patients with mutant and wild-type EZH2 relapsed/refractory DLBCL or FL, the interim data for 92 evaluable patients with FL showed an ORR of 74% in the group with mutated disease (n = 39) and 34% in the group with wild-type disease (n = 53).\textsuperscript{13} "I think it’s an exciting drug, not just because of [the efficacy data] but because it’s extremely well tolerated. The AE profile is almost nonexistent," Pagel said, adding that the drug has not been shown to cause significant myelosuppression, gastrointestinal toxicity, or rash and that no major safety signals have been observed.

Pagel said the next step will be evaluating tazemetostat in various combination regimens. “The company that’s sponsoring tazemetostat is now going to be looking at it in combination with R² as an obvious partner, so there will be a randomized trial of R² versus R² and tazemetostat. And that’s maybe where the field is evolving,” he said.

In addition to assessing tazemetostat with R², Epizyme, the company developing the agent, announced it also has plans to launch trials of tazemetostat in combination with rituximab for patients with relapsed/refractory FL and in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone as a frontline treatment for high-risk patients with FL.\textsuperscript{14} ■

"For the first time in a long time, we’re starting to get a more unified approach to the treatment of FL.”

—IAN W. FLINN, MD, PHD

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

Fulphila® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Fulphila® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

**IMPORTANT SAFETY INFORMATION**

Do not administer Fulphila® to patients with a history of serious allergic reactions, including anaphylaxis, to pegfilgrastim or filgrastim. Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila®.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila® for ARDS. Discontinue Fulphila® in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure and can recur within days after discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila® in patients with serious allergic reactions to any pegfilgrastim or filgrastim products.

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue if sickle cell crisis occurs.

Glonerulonephritis has been reported in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after withdrawal of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose reduction or interruption of Fulphila®. White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

Capillary leak syndrome has been reported after granulocyte colony-stimulating factor (G-CSF) administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

The G-CSF receptor, through which pegfilgrastim and filgrastim products act, has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., C-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology and discontinue Fulphila® if aortitis is suspected. Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results. The most common adverse reactions (≥ 5% difference in incidence) in placebo-controlled clinical trials are bone pain and pain in extremity.

**FULPHILA® (pegfilgrastim-jmdb) injection, for subcutaneous use**

**INDICATIONS AND USAGE**

**Patients with Cancer Receiving Myelosuppressive Chemotherapy**

Fulphila is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia [see Clinical Studies].

**Limitations of Use**

Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

**CONTRAINDICATIONS**

Fulphila is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products [see Warnings and Precautions]. Reactions have included anaphylaxis [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS**

**Splenic Rupture**

Spleenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila.

**Acute Respiratory Distress Syndrome**

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila, for ARDS. Discontinue Fulphila in patients with ARDS.

**Serious Allergic Reactions**

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila in patients with serious allergic reactions. Do not administer Fulphila to patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products.

**Use in Patients with Sickle Cell Disorders**

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue Fulphila if sickle cell crisis occurs.

**Glonerulonephritis**

Glonerulonephritis has occurred in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose reduction or interruption of Fulphila.

**Leukocytosis**

White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

**Capillary Leak Syndrome**

Capillary leak syndrome has been reported after G-CSF administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

**Potential for Tumor Growth Stimulatory Effects on Malignant Cells**

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim products and filgrastim products act has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., C-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology and discontinue Fulphila if aortitis is suspected. Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results. The most common adverse reactions (≥ 5% difference in incidence) in placebo-controlled clinical trials are bone pain and pain in extremity.

**Fulphila and the Fulphila logo are registered trademarks of Mylan Institutional Inc.**

**Neulasta® is a registered trademark of Amgen Inc.**

**MYLAN and the Mylan logo are registered trademarks of Mylan Inc.**

© 2019 Mylan Institutional Inc. All Rights Reserved. PEG-2019-0059
symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., C-reactive protein and white blood cell count). Consider aortic dissection in patients who develop these signs and symptoms without known etiology. Discontinue Fulphila if aortic dissection is suspected.

Nuclear Imaging
Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the labeling:
- Spleenic Rupture [See Warnings and Precautions]
- Acute Respiratory Distress Syndrome [See Warnings and Precautions]
- Serious Allergic Reactions [See Warnings and Precautions]
- Use in Patients with Sickle Cell Disorders [See Warnings and Precautions]
- Glomerulonephritis [See Warnings and Precautions]
- Leukocytosis [See Warnings and Precautions]
- Capillary Leak Syndrome [See Warnings and Precautions]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [See Warnings and Precautions]
- Aortitis [See Warnings and Precautions]

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

Pegfilgrastim clinical trials safety data are based upon 932 patients receiving pegfilgrastim in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 16% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 829), lung and thoric cancers (n = 53) and lymphoma (n = 56) received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles. The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m² every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other. The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Pegfilgrastim Patients Compared to Placebo in Study 3

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo (N = 461)</th>
<th>Pegfilgrastim 6 mg SC on Day 2 (N = 467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>20%</td>
<td>31%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Leukocytosis
In clinical studies, leukocytosis (WBC counts > 100 x 10⁹/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pegfilgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Binding antibodies to pegfilgrastim were detected using a Biacore assay. The approximate limit of detection for this assay is 500 ng/mL.

Pre-existing binding antibodies were detected in approximately 6% (51/789) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

Postmarketing Experience
The following adverse reactions have been identified during post approval use of pegfilgrastim products. 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.
- Spleenic rupture and splenomegaly (enlarged spleen) [see Warnings and Precautions]
- Acute respiratory distress syndrome (ARDS) [see Warnings and Precautions]
- Allogenic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema, and flushing [see Warnings and Precautions]
- Sickle cell crisis [see Warnings and Precautions]
- Glomerulonephritis [see Warnings and Precautions]
- Leukocytosis [see Warnings and Precautions]
- Capillary Leak Syndrome [see Warnings and Precautions]
- Injection site reactions
- Sudden's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Aortitis [see Warnings and Precautions]

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Although available data with Fulphila or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from previous studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage or adverse maternal or fetal outcomes.
In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim of approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryolethality and spontaneous abortions occurred at 4 times the maximum recommended human dose (mg/m²) with signs of maternal toxicity (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

Data
Human Data
Retrospective studies indicate that exposure to pegfilgrastim is without significant adverse effect on fetal outcomes and neonotria. Preterm deliveries have been reported in some patients.

Animal Data
Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.
Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following three stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

Lactation
Risk Summary
There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Fulphila and any potential adverse effects on the breastfed child from Fulphila or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature. Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma [see Clinical Pharmacology and Clinical Studies].

Geriatric Use
Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

OVERDOSAGE
Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. Events of edema, pleural effusion, or ascites have been reported in a single patient who administered pegfilgrastim on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions [see Adverse Reactions].

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim products.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses up to 10 times the recommended human dose (e.g., based on body surface area).

PATIENT COUNSELING INFORMATION
Advisf the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). Advise patients of the following risks and potential risks with Fulphila:
- Spleenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome
- Aortitis

Instruct patients who self-administer Fulphila using the single-dose prefilled syringe of the:
- Importance of following the Instructions for Use.
- Dangers of using syringes
- Importance of following local requirements for proper disposal of used syringes.

Manufactured by:
Mylan GmbH
Steinhausen, Switzerland, CH-6312
U.S. License No. 2062
Product of India
Code No.: K9/DRUGS/KTX/2827/7/2006
Distributed by:
Mylan Institutional LLC
Rockford, IL 61103 U.S.A.

Revised: 9/2018
B:PEFLR-R2
PEG-2019-0005
“I AM AN ADDICT.”
That is how Michael J. Keating, MBBS, describes himself and his pursuit of a cure for chronic lymphocytic leukemia (CLL). He acknowledges that investigators, like him, don’t do what they do in search of fame or glory or awards because that pursuit is a lot less important than the actual work that they do. Plus, his golf game is suspect, he doesn’t paint, and he doesn’t read “intelligent books.”

That leaves his work, to which he continues to devote 50 to 60 hours a week “in pursuit of my happiness, and that’s because I can’t think of anything that I do better than CLL,” Keating said. His achievements in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston in the CLL setting, however, might never have come to fruition if it hadn’t been for a disagreement in academic pursuits.

Keating grew up poor in Melbourne, Australia. His father worked as a clerk in the post office for 54 years, leaving the family in a lower socioeconomic class. Although both of Keating’s parents left school at a young age—his father at age 14, his mother at age 12—they recognized the importance of an education, sending Keating and his 3 sisters to Catholic high schools.

His interest in medicine began to take shape when Keating accompanied his parents on their physician visits. He was struck during those visits by the type of patients who filled the waiting room. Their physician was a general practitioner who saw patients of all ages. It was an experience that would help Keating relate to the patients who received care through the public hospital system when he became a physician, and it also made him grateful for the opportunity that was given to him.

There were no pediatricians to speak of outside academic centers. The same doctor had to treat all diseases in all age groups. Keating thought a career in medicine was perfect for him because it wouldn’t be boring, “and I don’t like being bored,” he said.

Whether it was the desire to avoid boredom or his intellectual curiosity that compelled Keating, he went on to earn a scholarship to attend the University of Melbourne. The Australian government paid all the college fees and the scholarship included a book allowance. Because of Keating’s lower socioeconomic situation, he received a modest living allowance of A$100 a year.

After completing his internship in 1967 and his residency in 1968, he found himself with no clear subspecialty focus. Luckily, he had studied under Gordon Carl de Gruchy, MD, MBBS, chair of the Department of Medicine at St. Vincent’s from 1962 to 1969 and author of Clinical Haematology in Medical Practice. “He introduced me to the research environment in hematology. He was most interested in classical benign hematology,” said Keating.

LIFE TAKES A TURN
A Yiddish proverb suggests that “man plans and God laughs.” Shortly after Keating was appointed, the Medical Board of Australia changed its licensing requirements, and physicians who were going to treat patients affected by hematologic disorders would have to go back and take the hematology boards, Keating included. He had a growing family with 4 children, and the salary implications of that backward move would be detrimental. Keating pursued other employment opportunities and applied to go to the United States, seeking a fellowship from several cancer centers.

The University of Texas MD Anderson Cancer Center was the only one that said it would pay a salary, and Keating’s decision was made. In 1974, he enrolled in the hematology-oncology fellowship program. Looking back at his early years at MD Anderson, Keating says it opened his eyes and mind about the amount of knowledge he had regarding acute lymphocytic leukemia (ALL). “When I walked into my first meeting with Emil J. Freireich, MD, [a 2015 Giants of Cancer Care award winner] and his colleagues, I found that I had a primitive understanding of the disease. There were 3 or 4 outstanding acute leukemia experts in the group,” he said.

Initially, Keating found himself drawn to the study of cytogenetic classification in ALL, and a paper he authored identified the major cytogenetic groups that were known at the time. He was able to define that 20% of the patients who experienced complete remission ended up being cured of their acute myeloid leukemia. The paper included a discussion involving 20 patients who had more than
5-year complete remissions. At the time, there were only 16 other patients in the world who had similar experiences and had been reported, said Keating.

He eventually set up patient databases for all the leukemias so that every patient who underwent treatment for leukemia from 1965 onward could be tracked. It allowed the clinicians and investigators to predict the likely outcomes of conventional treatments at the time.

ENTER FLUDARABINE

These experiences set the stage for Keating’s involvement with fludarabine and its effect in ALL. In the acute setting, the objective for treatment was to reach the maximum tolerated dose. However, at high doses, patients taking fludarabine developed blindness, paraplegia, and semicomatose symptoms. If fludarabine were undergoing research today, it might be discarded because of its toxicity, said Keating.

“We had seen dramatic shrinkage in lymph glands and clearing of the peripheral blood, and it became very apparent that this was a very major new drug in lymphoid diseases.”

At the time, there was a change in leadership in the hematology department, and the new administrator informed Keating that fludarabine would not be moving forward as a single agent in ALL.

Keating thought his new boss did not have enough patient care experience to realize that when patients learn they that they have ALL, it is terrifying, life-changing news. “Patients have gone from being healthy to facing situations where up to 40% of them would not reach remission stage and would die within a year of diagnosis,” he said.

Keating told his boss that the patients who came to a place like MD Anderson were willing to contribute to research in any way they could, but first and foremost, “we have to make sure that they are receiving the best treatment that’s available. The care of the patient is more important than understanding the disease.” The administrator thought Keating had the wrong attitude and summarily replaced him.

Undaunted, Keating turned his interests toward the CLL setting, where comparatively little research was being done, and brought fludarabine to investigators there. “I was very fortunate to be able to collaborate with people in the Department of Experimental Therapeutics, including William Plunkett, PhD, Varsha Gandhi, PhD, and Peng Huang, MD, PhD. They were all interested in exploring the pharmacodynamics of fludarabine,” said Keating.

The sparsely populated research environment of CLL allowed Keating to explore potential combinations without a lot of administrative interference. The agent was shown to be better than conventional therapy. Eventually, combining it with cyclophosphamide (FC) demonstrated more benefit than single-agent therapy, and adding rituximab to create a triple combination (FCR) resulted in even greater improved outcomes.

When he thinks back on fludarabine’s history, Keating understands the importance of treating each drug as a gift to be explored. His stepwise, mechanism-based approach—that is, determining what fludarabine does to pathways, what it does to DNA, and what it does to the immune system—resulted in a thorough database that all clinicians were able to use and access. The added benefit of fludarabine was its positive effect in allogeneic stem cell transplantation and on graft-versus-host disease, the main cause of fatal outcomes.

Keating’s translational experience in Freireich’s research laboratory served as the foundation for his work in the CLL group. “I enjoy listening to our laboratory colleagues and investigators because physicians are fairly intelligent people and they like to learn new things,” said Keating. This is also a good way to avoid being bored.

He is most thankful, however, for the gift that fludarabine gave to him: “It allowed me to work with so many different colleagues with different interests.” It also presented a teachable moment to fellows as they cycled through the fellowship program, said Keating. “It allowed me to demonstrate to the fellows that what you know is only a small part of what you could truly know. If you keep pursuing the answers to clinical questions, you’ll enjoy your time and benefit the patients.” The group went from 40 referrals a year to 200 referrals in 18 months. One patient who benefited from continuous remission was the impetus for the creation of the CLL Global Research Foundation, initially spearheaded by Keating. Because CLL affects fewer people than breast, lung, or prostate cancer, it garners little research money. The patient offered $100,000 to fund continuing research if Keating could come up with matching funds. Keating set out on his fund-raising effort and reached the goal. The patient then suggested that Keating start a foundation, but Keating was hesitant because of his modest formative years.

The CLL Global Research Foundation now awards up to $3 million a year to fund ongoing CLL research and education initiatives.

“I CAN’T RETIRE”

Keating keeps a positive outlook on continuing developments in CLL. He cites the progress in unlocking genetics and the genome, but he cautions that investigators have sequenced only about 3% to 5% of the DNA in the body. Understanding the remaining 95% remains a challenge. He also is encouraged by the role of viruses in cancer and the possibility of DNA vaccines. With all the new developments on the horizon, Keating enjoys the challenge. “I can’t retire. It’s impossible,” he said. ■
Colleagues Honor Bernard Fisher as an “Icon of Oncology”

by JASON HARRIS

BERNARD FISHER, MD, a world-renowned physician–scientist, longtime chair of the National Surgical Adjuvant Breast and Bowel Project (NSABP), and a tenacious advocate for the scientific method who transformed breast cancer care, died October 16 at age 101.

In Fisher’s most famous findings, data from the NSABP B-04 trial published in 1971 showed that total mastectomy produced outcomes equal to the more invasive radical mastectomy for women with breast cancer. Five years later, results from NSABP B-06 revealed lumpectomy plus radiation treatment to be as effective as mastectomy.

Fisher’s findings were extremely controversial. Conventional wisdom at the time held that radical mastectomy—removal of all breast and nearby tissues—was the only appropriate treatment for breast cancer. Daniel A. Osman, MD, founder and former director of the Miami Breast Cancer Conference®, said in 2013 that US surgeons “hated” Fisher when he began performing lumpectomies. Osman said Fisher lived by the credo “In God we trust. All others require data.”

As time went on, Fisher came to be regarded as a pioneer who persevered through intense criticism to make fundamental improvements in the treatment of breast cancer. In 2013, he was among the inaugural winners of the Giants of Cancer Care® awards.

FELLOW GIANTS SALUTE HIS WORK
“Few people have completely changed the thinking and management of a disease. Dr Fisher is truly an icon of oncology who forever changed our approach to treating breast cancer,” Richard L. Schilsky, MD, senior vice president of the American Society of Clinical Oncology (ASCO) and a 2018 Giants of Cancer Care® award winner in the community outreach/education category, said in a news release. “It is somehow remarkable that he would leave us in October, during Breast Cancer Awareness Month.”

“All of oncology owes an enormous debt of gratitude to the contributions of Bernard Fisher. He instilled in us the passion for the randomized prospective clinical trial as a vehicle to define optimum therapy in the treatment of breast cancer and other solid tumors applying the scientific method,” Norman Wolmark, MD, Fisher’s longtime protégé and a 2017 Giants of Cancer Care® award winner for breast cancer, said in a news release.

“He delivered us from the age of tyranny when a single individual could dictate the therapy of a particular disease based on his own biased retrospective experience,” Wolmark said. “In the process, Bernard Fisher revolutionized our understanding of the biology of breast cancer. His seminal work has saved countless patient lives and has had an immeasurable effect in allaying suffering. I have lost a mentor, colleague, and friend, and the field of oncology has lost its noblest protagonist.”

In 1967, Fisher became chair of the NSABP and remained in that role until 1994. Under his leadership, the project validated the use of tamoxifen as a breast cancer treatment and introduced neoadjuvant chemotherapy to reduce tumor size. In 1992, Fisher and the NSABP initiated the first trial to test tamoxifen as a breast cancer prevention agent, concluding that the drug decreased the incidence of breast cancer and was appropriate for many women at increased risk for the disease.

Fisher spent most of his adult life connected to the University of Pittsburgh and its medical center (UPMC). He earned his medical degree there in 1943 and joined the staff as the first full-time member of the department of surgery. He was named to his final role at UPMC, Distinguished Service Professor of Surgery, in 1986.

Among his many accomplishments, Fisher won the David A. Karnofsky Memorial Award and Lecture in 1980, ASCO’s highest scientific honor. He served as ASCO president from 1992 to 1993 and won its Distinguished Service Award for Scientific Achievement in 1999 and its Statesman Award in 2007. In 2014, ASCO named him an Oncology Luminary, in celebration of the society’s 50th anniversary.

“In the world lost one of our brightest minds today,” said Mike Hennessy Jr, president and chief executive officer of MJH Life Sciences”. “To say that Bernard Fisher was a ‘Giant’ would be an understatement. What he did for patients with breast cancer was game changing—millions of patients are alive and living better lives today thanks to treatments he helped discover.”

He also won the American Association for Cancer Research Award for Lifetime Achievement in Cancer Research, the American Cancer Society’s Medal of Honor, and the Albert Lasker Clinical Medical Research Award. Presidents Jimmy Carter and Ronald Reagan appointed him to national advisory boards.

IN MEMORIAM

More on OncLive®
Full Profile on Dr Fisher
onclive.com/link/6577
Working **better together** in the **liver**

### Median PFS in the liver

<table>
<thead>
<tr>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>24</td>
</tr>
</tbody>
</table>

- **20.5** months
- **+ 7.9** months
- HR: **0.69**
- 95% CI **0.55–0.90**; **p=0.002**

### SIR-Spheres® Y-90 resin microspheres + chemo in mCRC

- Significantly improves median PFS in the liver by 7.9 months, from 12.6 to 20.5 months (p=0.002)\(^1\)

- 31% reduction in risk of progression in the liver (HR: 0.69; 95% CI 0.55–0.90; p=0.002)\(^1\)

**SIR-Spheres Y-90 resin microspheres – the only SIRT supported by Level 1 evidence**

---

\(^1\) Primary endpoint of Overall PFS was not met in this study.

---

**caution:** Federal (USA) law restricts this device to use by, or on the order of, a physician. SIR-Spheres Y-90 resin microspheres may only be introduced in a facility licensed or accredited by a body capable of handling therapeutic medical isotopes. This product is radioactive and should thus be handled in accordance with all applicable standards and regulations. Intended Use / Indications For Use: SIR-Spheres Y-90 resin microspheres are approved for use in Argentina, Australia, Brazil, Canada, the European Union (EEA), Italy, and several countries in Asia for the treatment of unresectable liver tumors. In the US, SIR-Spheres Y-90 resin microspheres have been granted Approval (PMA) from the FDA and are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with advanced, extrahepatic, metastatic, chemotherapy-resistant (mRCC) at TORS (Pivotal). Warnings / Precautions: Adverse events related to the microspheres in locations other than the intended hepatic tumor may result in local radiation damage. Due to the radioactivity and the significant consequence of mislocating the microspheres in situ, this product must be implanted by physicians who have completed the Sirtex ICE training program. A PFS trial of the upper abdomen immediately after implantation is recommended. Patients may experience abdominal pain immediately after administration and pain which may be required for 3 days. All patients should be advised to seek medical assistance if pain persists or is severe. The most common adverse events reported are abdominal pain, nausea, anorexia, fatigue, headaches, and diarrhea. Potentially serious effects due to exposure to high radiation include acute pancyclopenia, radiation pneumonia, acute gastritis, radiation hepatitis, and acute cholecystitis. Contraindications: SIR-Spheres Y-90 resin microspheres should not be implanted in patients who have either had previous external beam radiation therapy to the liver, or if there is a clinical liver failure. This device is contraindicated in patients with moderate to severe bowel obstruction (greater than 20% loss of the hepatic arterial blood flow determined on hepatic arteriography and disease, and portal vein thrombosis. This device should not be implanted in patients determined via angiography to have an abnormal vascular anatomy that would result in significant reflux of the hepatic arterial blood flow into the stomach, pancreas or bowel. Reference the Package Insert (www.sirtex.com) for a complete listing of indications, contraindications, side effects, warnings, and precautions.

**SIR-Spheres**® is a registered trademark of Sirtex SIR-Spheres Pty Ltd.