Adaptation Is Key to Advancing Care for Adult Patients With Leukemia

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By Julie E. Chang, MD
ARE YOU THINKING DEEP ENOUGH
IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too\(^1\)\(^2\)

With each relapse, multiple myeloma becomes increasingly difficult to control. As the disease progresses, very few patients (less than 5%) experience a deep response.\(^1\)\(^2\) However, evidence suggests a deep response may be associated with improved PFS and OS.\(^1\)\(^3\) Therefore, shouldn’t a goal of treatment be to achieve a deep response in as many patients as possible?

The hope is that more patients may achieve a deep response with emerging therapies on the horizon.

Learn more about why depth of response matters in relapsed or refractory multiple myeloma.

Visit ThinkDeepMM.com

\(^{GS}\) overall survival \(^{PFS}\) progression-free survival.

References:
MAURIE MARKMAN, MD
President
Medicine & Science
Cancer Treatment Centers of America
Philadelphia, PA

Jeffrey Crawford, MD
Duke University School of Medicine
Durham, NC

Roy S. Herbst MD, PhD
Smilow Cancer Hospital
Yale New Haven Health
New Haven, CT

Thomas Hutson, DO, PharmD
Texas Oncology/Baylor Charles A. Sammons Cancer Center
Dallas, TX

Melissa L. Johnson, MD
Sarah Cannon Research Institute/Tennessee Oncology
Nashville, TN

Elias Jabbour, MD
The University of Texas MD Anderson Cancer Center
Houston, TX

Richard W. Joseph, MD
Mayo Clinic Cancer Center
Jacksonville, FL

Mario E. Lacouture, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Corey J. Langer, MD
Penn Medicine
Abramson Cancer Center
Philadelphia, PA

Benjamin P. Levy, MD
Johns Hopkins Sidney Kimmel Cancer Center
Sibley Memorial Hospital
Washington, DC

Sagar Lonial, MD
Winship Cancer Institute of Emory University
Atlanta, GA

Michael A. Morse, MD, MHS
Duke University School of Medicine
Durham, NC

Howard S. Hochster, MD
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ

Debu Tripathy, MD
The University of Texas MD Anderson Cancer Center
Houston, TX

Tanios Bekaii-Saab, MD, FACP
Mayo Clinic Cancer Center
Rochester, MN

Ghassan K. Abou-Alfa, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Andrew D. Seidman, MD
Memorial Sloan Kettering Cancer Center
New York, NY

Michael J. Birrer, MD, PhD
Institute/Tennessee Oncology
Nashville, TN

Sarah Cannon Research Institute/Tennessee Oncology
Nashville, TN

Lee S. Schwartzberg, MD
West Cancer Center
Germantown, TN

Jennifer S. Weber, MD, PhD
NYU Langone Medical Center
New York, NY

Ashish K. Kalkanis, MD
Memorial Sloan Kettering Cancer Center
New York, NY

James L. Moore, MD
University of Texas Southwestern Medical Center
Dallas, TX

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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 78.
Adaptation Is Key to Advancing Care for Adult Patients With Leukemia

by ANDREW D. SMITH

As a respected innovator and thought leader, Jorge E. Cortes, MD, has helped facilitate the development of the robust array of therapies available today for treating patients with leukemia. Cortes discussed emerging developments in the field in advance of the 26th Annual International Congress on Hematologic Malignancies®. He is serving as a cochair of the conference, which Physicians’ Education Resource®, LLC (PER®) is sponsoring February 24 through February 27, 2022, in Miami Beach, Florida.
**INDICATIONS**

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

CABOMETYX is indicated for the treatment of patients with advanced RCC.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

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

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

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

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

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

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

**Hepatotoxicity:** CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 25 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

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

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

**Proteinuria:** Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for...
A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.3,4


For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages. 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.
5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX-treated patients in the RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 4 or higher hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melaena.

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

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in 0.4% of CABOMETYX-treated patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

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

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX. Monitor and manage patients using anti-diarrheals as indicated. Withhold CABOMETYX until improvement to Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmoplantar Erythrodysesthesia
Palm-planter erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drug is used as a single agent. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was observed in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=16) or nivolumab (n=17) as a single agent or with both (n=11), recurrence of Grade ≥2 increased ALT or AST was observed in 72% (n=32), 88% (n=14), and 48% (n=6), respectively. CABOMETYX was reduced in 19% of patients treated with CABOMETYX with nivolumab which was withfirmed for adverse renal insufficiency. 6 reinitiated treatment after symptom improvement; of these, (n=9) received hormone replacement therapy and 2 had recurrence of adverse renal insufficiency.

5.9 Proteinuria
Proteinuria was observed in 8% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients with nephrotic syndrome.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX. ONJ can manifest as jaw pain, osteomyelitis, osseous, bone erosion, tooth or periodontal infection, fistula, gingival ulceration or erosion, persistent pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until resolution, resume at a reduced dose.

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

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Perform an evaluation for RPLS in any patient presenting with headaches, seizures, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.13 Thyroid Dysfunction
Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 2% of patients treated with CABOMETYX, including Grade 3 in 0% of patients. Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

6. CONTRAINDICATIONS
CABOMETYX is contraindicated for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX, in combination with nivolumab, is contraindicated for the first-line treatment of patients with advanced RCC.

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

6.2 Differentiated Thyroid Cancer
CABOMETYX is contraindicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (dTC) that has progressed following prior VEGF-targeted therapy and who are radioactive iodine-refractory or ineligible.

6.4 CONTRAINDICATIONS
In the randomized, open-label trial in which 337 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity, patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-planter erythrodysesthesia (PPE), hyperglycemia, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, PPE, hyperglycemia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% of patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).
CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥25%) in patients treated with CABOMETYX were hypertension, diaphoresis, hypophosphatemia, PPE, fatigue, increased ALT decreased appetite, stomatitis, pain, hypotenison, and syncope. The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 40% of patients receiving CABOMETYX, and in 30% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on prior treatment, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥ 1% Patients Who Received CABOMETYX in CABOSUN

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=78)</th>
<th>Sunitinib (n=72)</th>
<th>Grade 3-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any Grade 3-4 Adverse Reaction</td>
<td>68</td>
<td>65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatotoxicity (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
<th>Grade 3-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any Grade 3-4 Laboratory Abnormality</td>
<td>88</td>
<td>65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab. The most frequent (≥2%) serious adverse reactions were diarrhea, hypertension, PPE, stomatitis, rash, rash, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, vomiting, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥1% of Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=320)</th>
<th>Sunitinib (n=320)</th>
<th>Grade 3-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any Grade 3-4 Laboratory Abnormality</td>
<td>50</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adverse Reaction

Leading to dose interruption occurred in 84% of patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 6. Adverse Reactions Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>66%</td>
<td>2%</td>
</tr>
<tr>
<td>AST increased</td>
<td>66%</td>
<td>2%</td>
</tr>
<tr>
<td>LDH increased</td>
<td>77%</td>
<td>7%</td>
</tr>
<tr>
<td>GGT increased</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51%</td>
<td>3%</td>
</tr>
<tr>
<td>Rash</td>
<td>48%</td>
<td>2%</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>21%</td>
<td>9%</td>
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Table 7. Laboratory Abnormalities Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL

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</tbody>
</table>

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81.1% male, 56.7% White, and had a median age of 64 years.

Adverse reactions occurring in ≥25% of CABOMETYX- treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grades 3-4 adverse reactions which occurred in ≥5% of patients were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 8. Laboratory Values Worsening from Baseline

<table>
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<th>Laboratory Abnormality</th>
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<tr>
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</tbody>
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Table 9. Laboratory Abnormalities Occurring in ≥25% of CABOMETYX-Treated Patients in COSMIC-311

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
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</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>66%</td>
<td>2%</td>
</tr>
<tr>
<td>AST increased</td>
<td>66%</td>
<td>2%</td>
</tr>
<tr>
<td>LDH increased</td>
<td>77%</td>
<td>7%</td>
</tr>
<tr>
<td>GGT increased</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51%</td>
<td>3%</td>
</tr>
<tr>
<td>Rash</td>
<td>48%</td>
<td>2%</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>21%</td>
<td>9%</td>
</tr>
</tbody>
</table>
9.2 Lactation
Risk Summary
There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

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

Contraception
CABOMETYX can cause fetal harm when administered to a pregnant woman. Females
Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility
Females and Males
Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older. Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure was similar across all ages.

Juvenile Animal Toxicity Data
Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Toxicities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/dl based on body surface area). Hypocalcemia was observed at doses ≥1 mg/kg/day (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testes persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older. In CABOSUN and METEOR, 41% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMate-648, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and Fistula: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diabetes: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms of osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to contact their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new or worsening neurological function.

Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.

Embryo-fetal toxicity:

• Advise females of reproductive potential of the potential risk to a fetus.
• Advise females to inform their healthcare provider of a pregnancy or a possibility of pregnancy.

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

• Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John’s wort.

Important administration information
Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information
Revision 10/2021
Distributed by Exelixis, Inc. Alameda, CA 94502

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Printed in USA 10/2021 CA-11214-1
Leukemia Landscape Shows Hallmarks of Success

WHEN JORGE E. CORTES, MD, began his career in oncology more than 30 years ago, there were few therapeutic options for adult patients with leukemia and those regimens had limited efficacy. Fast forward to today, when the treatment toolkit is stocked with novel therapies for a range of hematologic malignancies. Cortes, who is featured in the cover story in this issue of OncologyLive®, has been an integral part of that success story.

Cortes joined the faculty at The University of Texas MD Anderson Cancer Center in Houston in the late 1990s. Those were heady times in the field. Investigators at the center were participating in the initial studies that paved the way for the FDA’s 2001 approval of imatinib (Gleevec) for patients with chronic myeloid leukemia (CML), which helped usher in the targeted therapy era in oncology.1,2 Hagop M. Kantarjian, MD, a member of the imatinib research team who was honored with a 2014 Giants of Cancer Care® award in the leukemia category, was building one of the world’s largest and most respected leukemia departments at MD Anderson.

As a clinical investigator in that department, Cortes helped develop programs that led to FDA approvals for several drugs, including bosutinib (Bosulif) and ponatinib (Iclusig) for patients with CML and glasdegib (Daurismo) for patients 75 years and older with acute myeloid leukemia.

Cortes is now an oncology leader in a different mode. In 2019, he became director of the Georgia Cancer Center at Augusta University, where he is working to enhance basic science, translational research, and clinical trial programs.

Throughout his career, Cortes has contributed to advances in cancer care by evaluating new strategies as evidence-based findings became available and making adjustments in his approach. He will share his knowledge about emerging developments in the field during the 26th Annual International Congress on Hematologic Malignancies® that Physicians’ Education Resource® (PER®), LLC, is hosting February 24 through February 27, 2022, in Miami Beach, Florida. Cortes will serve as a cochair of the hybrid interactive conference.

The meeting will be one of the first continuing medical education conferences on the PER® 2022 calendar. Cortes, of course, will be an invaluable resource for practicing hematologists seeking to learn about the intricacies of treating patients with leukemias in the modern oncology era. We’ll have live coverage from this conference and other meetings, such as the 2021 American Society of Hematology Annual Meeting, on OncLive.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
Cardinal Health™ Navista™ TS

Predict episodic care costs.
Track value-based performance.

Built by Fuse, the innovation engine of Cardinal Health, Episode Analytics is a first-of-its-kind predictive analytics tool that gives you an accurate view from the start.

**Predict** the cost at the onset of care

**Track** costs throughout the episode of care

Episode Analytics is delivered as part of Cardinal Health™ Navista™ Tech Solutions (TS), an integrated suite of tech solutions for value-based care.

Scan the QR code or visit cardinalhealth.com/navista to learn more and request a demo.

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Oncology Drug Regulation Faces an Uncertain Future

by MAURIE MARKMAN, MD

The stunningly successful rapid development of safe and effective vaccines to combat COVID-19 sends an encouraging message that industry, sometimes with the support of government agencies, can quickly create agents that are of unquestionable benefit for mankind. The message underscores the potential for pharmaceutical developments in a wide range of human illnesses.

The basic, translational, and clinical science activities conducted over the past 2 years that led to the development of the vaccines and potentially novel medications to treat active COVID-19–related illness must be lauded. However, formidable challenges ahead also must be acknowledged. Perhaps most concerning is that scientists are being attacked across the globe for stating their views regarding the evolving evidence related to the pandemic.

It has been widely reported that Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases received death threats that resulted in a security detail being assigned to Fauci and his family. In a survey of more than 300 scientists conducted by *Nature*, 15% reported receiving death threats. The potential negative effects associated with social media–generated activity on open scientific discourse cannot be overstated.

Further, the political atmosphere in the United States has made essential coordinated efforts by public health agencies problematic. For example, it is more than 9 months into the new presidential administration and a permanent director for the FDA still has not been appointed. This may have contributed to less-than-optimal timely review of critical COVID-19–related decisions, impaired public communication efforts, and confusing regulatory decisions, such as the widely disputed approval of the Alzheimer disease drug aducanumab (Aduhelm).

The FDA will be confronted with major challenges in the coming years, including some that the agency has internally identified. Examples include evidence that the magnetic fields of smartphones and smartwatches may interfere with pacemakers and cardiac defibrillators and concerns that clinical trials of innovative surgical tools being explored in cancer care (eg, robotically assisted surgical devices for mastectomy) may not adequately examine essential issues of patient safety.

The FDA Oncology Center of Excellence Scientific Collaborate is working to focus the efforts of the agency on both current and future needs of patients with cancer and on maintaining awareness of the rapidly evolving and often increasingly complex science. Particularly noteworthy are defined plans in precision oncology, pediatric cancers, rare cancers, oncologic safety, patient-focused drug development, and innovative trial designs.

The FDA will need to continue to confront the reality that treatment is being increasingly based on defining molecular pathways rather than the site of origin of the cancer or the histological subtype. For example, if a drug with molecularly inhibitory effects demonstrates high clinical activity in resistant metastatic tumors from the breast, will investigators need to demonstrate the same degree of clinical activity of the agent in a clinical trial for other tumors with the identical resistant cancer phenotype?

Similarly, it is likely that molecularly defined resistance mechanisms rather than site of origin–based treatment programs will comprise a major component of pharmaceutical anticancer agents up for regulatory approval. Apart from the widely recognized mechanisms of resistance, the FDA also will need to consider efficacy outcomes against smaller subsets of well-characterized resistance mutations (eg, rare *EGFR* mutations).

The FDA will need to consider the future of several areas of clinical trial design. These include the requirement of an objectively meaningful study control arm, the potential need to permit crossover from the control to the experimental arm, and the use of patient-reported outcomes.
to the investigative regimen at the time of disease progression, and relevant or acceptable study end points for regulatory approval.

Additionally, the agency should recommend the enrollment of individuals who represent appropriate patient populations with the malignancy—elderly patients, patients with common clinically relevant comorbidities, and patients from varied socioeconomic and ethnic groups. In terms of safety analysis for investigational and maintenance therapies, investigators should evaluate the effect of low-grade adverse events on patient quality of life until documented disease progression.

Finally, it is relevant to note the pushback the FDA faces from those who challenge the current approach to trial design leading to regulatory approval,4 and also to note the clinical value of examining real-world outcomes vs the typical nonreal-world participants whom are often enrolled in cancer clinical trials.5

As cancer becomes treated in a number of settings as a serious but chronic condition, the objective of investigators to demonstrate an improvement in overall survival becomes increasingly problematic. In this clinical scenario, patients may receive several therapies after experiencing disease progression, 1 or more of which may favorably affect an individual’s survival.

Despite the complexity of the task, the role of the FDA in the cancer arena has never been more relevant. Agency leaders should be encouraged to improve regulatory science, include a patient’s perspective in approval decisions, reduce unnecessary bureaucracy and costs associated with the conduct of trials, and accelerate the overall review process for drug approval.

REFERENCES


Abemaciclib, Endocrine Therapy Moves Ahead for Select Early Breast Cancer

The FDA has approved abemaciclib (Verzenio) in combination with endocrine therapy in the form of tamoxifen or an aromatase inhibitor (AI) for the adjuvant treatment of adult patients with hormone receptor-positive, HER2-negative, early breast cancer at high risk of recurrence and a Ki-67 score of 20% or higher, as determined by an FDA-approved test.

Efficacy was evaluated in the phase 3 monarchE trial (NCT03155997). Among the 2003 patients with a high risk of recurrence and a Ki-67 score of 20% or higher, there was a statistically significant improvement in invasive disease-free survival (iDFS; HR, 0.62; 95% CI, 0.50-0.81; P = .0042). At 36 months, the iDFS rate was 86.1% (95% CI, 82.8%-88.8%) for patients receiving abemaciclib plus tamoxifen or an AI (n = 1017) vs 79% (95% CI, 75.3%-82.3%) for those receiving tamoxifen or an AI alone (n = 986). Overall survival data were not mature at the time of iDFS analysis.

The FDA simultaneously approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) test for use as a companion diagnostic. This is the first immunohistochemistry test measuring Ki-67 expression to receive regulatory approval in the context of treatment with abemaciclib, according to Agilent Technologies Inc, which developed the assay in collaboration with Eli Lilly and Company.

TO READ MORE, VISIT bit.ly/3AH4kcI and bit.ly/2XCXAAA1

Clinical Hold Is Lifted for Rusfertide Clinical Development Program

The FDA has removed the full clinical hold from trials evaluating rusfertide (PTG-300), an injectable synthetic mimetic of hepcidin, allowing dosing on all studies assessing this agent to resume.

In response to the hold, the pharmaceutical company provided individual patient data safety reports, along with updated investigator brochure and patient-informed consent forms. A comprehensive review of the most recent safety database, including cases of suspected unexpected serious adverse reactions. No additional cancer cases and no other unexpected safety signals surfaced in the process.

Moreover, the objective response rate was 68% (95% CI, 62%-74%) in the pembrolizumab arm vs 50% (95% CI, 44%-56%) in the placebo arm; the median durations of responses were 18.0 and 10.4 months, respectively.

TO READ MORE, VISIT bit.ly/3vgAomWx.
BETTER IS HOME TO NEW JERSEY’S BEST CANCER CENTER

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

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
Drug Spotlight | BREXUCABTAGENE AUTOLEUCEL (TECARTUS)

Brexucabtagene Autoleucel Expands Treatment Possibilities in ALL

by KYLE DOHERTY

BASED ON DATA FROM the phase 1/2 ZUMA-3 trial (NCT02614066), the FDA has approved the CD19-directed chimeric antigen receptor (CAR) T-cell immunotherapy brexucabtagene autoleucel (Tecartus) for the treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

In 54 evaluable patients, 51.9% (95% CI, 37.8%-65.7%) achieved complete remission (CR) within 3 months of infusion. The overall CR rate, comprising CR rate and CR with incomplete blood count (CRi) recovery rate, was 64.8% (95% CI, 51%-77%).

In an interview with OncologyLive®, Bijal Shah, MD, MS, an associate member of the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida, discussed the results of the trial and how this approval will enhance the treatment of patients with relapsed or refractory B-cell precursor ALL.

Q Please describe the trial design of ZUMA-3.

This was a study of CAR-T cell immunotherapy for patients who had failed 2 lines of therapy or whose disease was primary refractory. We left the definition of what qualifies as primary refractory up to the investigator, [but participants] could include individuals who had no response to frontline therapy or individuals who were relapsing very quickly. Approximately one-third of patients were primary refractory and the rest had disease relapse after 2 or more lines of therapy.

The median number of prior lines of therapy was 2, with some patients having received up to 8. Approximately 40% of patients had [either] prior allogeneic stem cell transplant or [treatment with] blinatumomab [Blincyto]. By and large, these are heavily pretreated patients. They had to have morphologic disease [in bone marrow] and had to have at least 5% [bone marrow] blasts. The median [rate] of bone marrow blast was approximately 60% for those enrolled. [These patients had] fairly hefty tumor burden.

Q What were some of the key findings from ZUMA-3?

We observed a little [more than] 70% in terms of the CR/CRi rate. It’s really exciting. The majority of these remissions were true CRs, approximately 56%. For those who achieved a CR/CRi, the median duration of response was a little [more than] 12 months. With approximately 60 months of follow-up, a little [more than] 30% of patients were still experiencing an ongoing CR. We feel [these are] pretty powerful data and are excited that the FDA agrees.

[Further, the] median overall survival was 18.2 months. In this population of patients with primary refractory disease, multiple relapsed disease, or heavily pretreated disease, this is unheard of. We have not achieved this magnitude of overall survival in any of our previous trials. This is very exciting to me. It means we’re finally able to bring a therapy with tremendous potential to mediate an antitumor response, as we’ve seen in large B-cell lymphoma and mantle cell lymphoma, into ALL.

Q What adverse events should clinicians be aware of when prescribing brexucabtagene autoleucel?

When we talk about risks with brexucabtagene autoleucel, we talk about them largely in the context of what we expect when we overactivate the immune system. These include CRS [cytokine release syndrome], fever, hypertension, and in some cases organ injury. With intervention with tocilizumab [Actemra] and/or steroids, we were able to push the rate of CRS down to approximately 25% [incidence] in terms of severe [adverse] events. I’m very happy with where we’ve landed, but certainly there’s room to do better.

The same goes for neurologic toxicities. This is where we’ve made our biggest dent, perhaps more than with CRS. It’s hard to know [exactly], but we were able to reduce the rate to approximately 25% for severe neurotoxicity. [In results of other studies of CAR T-cell therapy] in adults with ALL, the rate of severe neurotoxicity is in the 40% range. We did have 1 death from neurotoxicity, [which was] a case of brain edema with herniation.

It’s important to stress that there can still be rare events that culminate in bad outcomes. We also saw evidence of sepsis and infection as you might otherwise see in someone who is receiving therapy. When we look at all these events, what we’re seeing in terms of CAR T-cell therapy and the toxicity observed, [is that it] still low relative to what we might see with other agents.

Q What does the future hold for brexucabtagene autoleucel?

One of the things we might try to do as we move forward is figure out how to implement this therapy in earlier lines and [for patients] with lower disease burden. [IF] we can [treat patients] when they are less sick we can worry less about an infection. [Additionally,] with that lower disease burden we’re going to get better CAR T-cell expansion. We saw that in [ZUMA-3]—those with down to 5% blast had lower toxicity. That’s the perfect formula of low toxicity and high efficacy that we want for this therapy.

We must be open to exploring these options. When I talk about the future, it’s not 5 years from now, it’s now. We have these incredible therapies that are at our disposal. I’m looking forward to seeing how this plays out and excited that we get to add this new therapy to our treatment paradigm.

Q In light of this approval, is there anything you would emphasize to treating clinicians referring patients for therapy?

It’s always the same advice: refer early. There are things that we do in the academic setting—whether it’s molecular MRD [minimal residual disease] testing or more comprehensive genetic testing of the leukemia—to try to predict what’s coming [for patients] or to try to understand how to optimize novel agents, and now CAR T-cell therapy as part of that treatment paradigm. Referring early is the secret to having access to all these approaches for our patients. It really opens the door. We have an ability to better adapt to how unpredictable this disease can be. That’s what my colleagues [and I] want to be able to do, to help assist in the care of these patients.

REFERENCES

FDA grants approval to brexucabtagene autoleucel (Tecartus) for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

**Mechanism of action:**
- Brexucabtagene autoleucel is a CD19-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell immunotherapy that binds to CD19-expressing cancer cells and normal B cells.

**How supplied:**
- Cell suspension for infusion (approximately 68 mL)

**Dose:**
- $1 \times 10^6$ CAR-positive viable T cells per kg of body weight, with a maximum of $1 \times 10^8$ CAR-positive viable T cells
- Do not use a leukodepleting filter.
- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion
- Premedicate with acetaminophen and diphenhydramine
- Confirm availability of tocilizumab prior to infusion

**BASELINE CHARACTERISTICS: PATIENTS RECEIVING BREXUCABTAGENE AUTOLEUCEL**

- Median age, years (range)
  - 40 (19-84)
- Median time from leukapheresis to product delivery
  - 00 16 DAYS

**Box Warning**
- Cytokine release syndrome (CRS): Life-threatening reactions have occurred in some patients receiving brexucabtagene autoleucel. Do not administer treatment to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities: Life-threatening reactions have occurred in some patients receiving brexucabtagene autoleucel, concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment and provide supportive care and/or corticosteroids as needed.

**Efficacy Results in ZUMA-3 Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Brexucabtagene autoleucel (n=54)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCR rate (95% CI)</td>
<td>64.8% (51%-77%)</td>
</tr>
<tr>
<td>CR rate (95% CI)</td>
<td>51.9% (37.8%-65.7%)</td>
</tr>
<tr>
<td>Median duration of remission, months (95% CI)</td>
<td>13.6 (9.4-NE)</td>
</tr>
<tr>
<td>Median DOR, if best response is CR, months (95% CI)</td>
<td>NR (9.6-NE)</td>
</tr>
<tr>
<td>Median DOR, if best response is CRi, months (95% CI)</td>
<td>8.7 (1.0-NE)</td>
</tr>
</tbody>
</table>

* Efficacy evaluable population.

**WARNINGS AND PRECAUTIONS**

- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
- Hypersensitivity reactions
- Severe infections
- Prolonged cytopenias
- Hypogammaglobulinemia
- Secondary malignancies
- Effects on ability to drive and use machines

**COMMONLY REPORTED ADVERSE EFFECTS IN ZUMA-3 TRIAL**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Brexucabtagene autoleucel (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>96% 38%</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>92% 26%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>69% 33%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>63% 27%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>63% 6%</td>
</tr>
</tbody>
</table>

**REFERENCE**

INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:
• adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
• adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
• adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

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

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

### Treatment naive (n=39)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>CR + PR</th>
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<tr>
<td>Advanced or Metastatic RET-Fusion-Positive NSCLC</td>
<td>85%</td>
<td>0% + 85%</td>
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<tr>
<td>Median DoR not yet reached</td>
<td>12%</td>
<td>95% CI: 70, 94</td>
</tr>
<tr>
<td>median follow-up: 7.4 months</td>
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### Previously treated with platinum chemotherapy (n=105)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>CR + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced or Metastatic RET-Mutant MTC</td>
<td>64%</td>
<td>1.9% + 62%</td>
</tr>
<tr>
<td>Median DoR was 17.5 months</td>
<td>12%</td>
<td>95% CI: 54, 73</td>
</tr>
<tr>
<td>median follow-up: 12.1 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases

CNS DoR was ≥6 months in all responders with measurable brain metastases

No patients received radiation therapy to the brain within 2 months prior to study entry

### Advanced or Metastatic RET Fusion-Positive Thyroid Cancer (Non-MTC)

<table>
<thead>
<tr>
<th>Systemic therapy naïve (n=8)</th>
<th>ORR</th>
<th>CR + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib/vandetanib</td>
<td>100%</td>
<td>12.5% + 88%</td>
</tr>
<tr>
<td>Median DoR not yet reached</td>
<td>16%</td>
<td>95% CI: 63, 100</td>
</tr>
<tr>
<td>median follow-up: 8.8 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Advanced or Metastatic RET-Mutant MTC

<table>
<thead>
<tr>
<th>Previously treated (n=19)</th>
<th>ORR</th>
<th>CR + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib/vandetanib</td>
<td>79%</td>
<td>5.3% + 74%</td>
</tr>
<tr>
<td>Median DoR was 18.4 months</td>
<td>16%</td>
<td>95% CI: 54, 94</td>
</tr>
<tr>
<td>median follow-up: 17.5 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Advanced or Metastatic RET-Mutant MTC

<table>
<thead>
<tr>
<th>Previously treated with cabozantinib and/or vandetanib (n=55)</th>
<th>ORR</th>
<th>CR + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>69%</td>
<td>9% + 60%</td>
<td></td>
</tr>
<tr>
<td>Median DoR not yet reached</td>
<td>16%</td>
<td>95% CI: 55, 81</td>
</tr>
<tr>
<td>median follow-up: 14.1 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

#### Trial Design
The phase I/II, multicohort, open-label, single-arm, multicenter LIBRETTO-001 trial evaluated the efficacy of Retevmo in a population of 702 patients with metastatic RET fusion-positive NSCLC (n=332), advanced or metastatic RET fusion-positive thyroid cancer (n=38), advanced or metastatic RET-mutant MTC (n=306), and certain other advanced solid tumors with RET alterations (n=26). The study enrolled the following cohorts: systemic therapy-naive patients (n=59) and previously treated (n=105) patients who had progressed on platinum-based chemotherapy with metastatic RET fusion-positive NSCLC, systemic therapy-naive (n=81) and previously treated (n=190) patients with advanced or metastatic RET fusion-positive thyroid cancer (non-MTC), and treatment-naive (n=88) and previously treated (n=55) patients with advanced or metastatic RET-mutant MTC. Major efficacy outcomes were ORR and DoR. In phase II, the dose for Retevmo was 160 mg PO BID. ORR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v1.1. All results reviewed by an IRC.

### Adverse Reactions and Laboratory Abnormalities

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

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PP-SE-US-0397 11/2020 © Lilly USA, LLC 2020. All rights reserved.
Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTc interval to >500 ms was measured in 6% of patients and an increase in the QTc interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

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

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

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

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

Severe adverse reactions (Grade 3-4) occurring in >15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.2%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

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

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

RETevmo™ (selpercatinib) capsules, for oral use
Initial U.S. Approval: 2020

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

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

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

Monitor ALT and AST prior to initiating RETevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Without, reduce dose or permanently discontinue RETevmo based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 11% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.

Do not initiate RETevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETevmo. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETevmo based on the severity.

QT Interval Prolongation
RETevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >550 ms was measured in 6% of patients and an increase in the QTcF interval of at least 80 ms over baseline was measured in 15% of patients. RETevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infection.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia/arrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diabetes, Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETevmo and during treatment.

Monitor the QT interval more frequently when RETevmo is concurrently administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETevmo based on the severity.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETevmo. Grade ≥ 3 hemorrhagic events occurred in 2.3% of patients treated with RETevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

Permanently discontinue RETevmo in patients with severe or life-threatening hemorrhage.

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

If hypersensitivity occurs, withhold RETevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETevmo at a reduced dose and increase the dose of RETevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETevmo for recurrent hypersensitivity.

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

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

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

ADVERSE REACTIONS

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

RET Gene Fusion or Gene Mutation Positive Solid Tumors
The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETevmo as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001. Among 702 patients who received RETevmo, 65% were exposed for 6 months or longer and 34% were exposed for greater than one year. Among these patients, 95% received at least one dose of RETevmo at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (41%), mTC (44%), and non-medullary thyroid carcinoma (5%).

Serious adverse reactions occurred in 33% of patients who received RETevmo. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥ 1 patient included sepsis (n = 3), cardiac arrest (n = 3) and respiratory failure (n = 3).

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received RETevmo. Adverse reactions resulting in permanent discontinuation included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

Dose interruptions due to an adverse reaction occurred in 42% of patients who received RETevmo. Adverse reactions requiring dosage interruption included increased ALT (0.4%), increased AST, increased hypertension, diarrhea, pyrexia, and QT prolongation.

Dose reductions due to an adverse reaction occurred in 31% of patients who received RETevmo. Adverse reactions requiring dosage reductions included increased ALT (0.4%), increased AST, increased hypertension, diarrhea, pyrexia, QT prolongation and fatigue.

The most common adverse reactions, including laboratory abnormalities, (≥ 25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hyperventilation, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

Table 1 summarizes the adverse reactions in LIBRETTO-001.

| Table 1: Adverse Reactions (≥15%) in Patients Who Received RETevmo in LIBRETTO-001 |
|-----------------------------------------------|-----|-----|
| **Adverse Reaction** | RETevmo (n=702) |
| **Grades 1-4 (%)** | **Grades 3-4 (%)** |
| **Gastrointestinal** | |
| Dry Mouth | 39 | 0 |
| Diarrhea | 37 | 3.4 |
| Constipation | 25 | 0.6 |
| Nausea | 23 | 0.6 |
| Abdominal pain | 23 | 1.9 |
| Vomiting | 15 | 0.3 |
| **Vascular** | |
| Hypertension | 35 | 18 |

RETevmo™ (selpercatinib) capsules, for oral use
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RETevmo™ (selpercatinib) capsules, for oral use
SE HCP BS 08MAR2020
Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

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

1 Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence.
2 Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.
3 Fatigue includes fatigue, asthenia, malaise.
4 Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling face, eye swelling, peripheral swelling.
5 Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic.
6 Headache includes headache, sinus headache, tension headache.
7 Includes cough, productive cough.
8 Includes dyspea, dyspea exertional, dyspea at rest.
9 Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hæmatoechæ, pethiche, traumatic hæmatoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, spontaneous hæmatoma, abdominal wall hæmatoma, angina biliaris hæmorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic anæmia, intradominal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, pelvic hæmatoma, periorbital hemorrhage, pharyngeal hemorrhage, pulmonary contusion, purpura, retroperitoneal hæmatoma, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hæmatoma.

Only includes a grade 3 adverse reaction.

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

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
</tr>
</tbody>
</table>

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

Increased Creatinine

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

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

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

Strong and Moderate CYP3A Inhibitors

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

Strong and Moderate CYP3A Inducers

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

Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

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

Drugs that Prolong QT Interval

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

Lactation

Risk Summary

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

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

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

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

Pediatric Use

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

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

Animal Toxicity Data

In 4-week general toxicology studies in rats, animals showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures > approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (>1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Geriatric Use

Of 702 patients who received RETEVMO, 34% (239 patients) were ≥65 years of age and 10% (67 patients) were >75 years of age. No overall differences were observed in the safety or effectiveness of RETEVIMO between patients who were ≥65 years of age and younger patients.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CrCl] >30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease.

Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

Rx only.

Additional information can be found at www.retevmo.com.

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RETEVMO™ (selpercatinib) capsules, for oral use

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Atezolizumab Provides Option for Patients With NSCLC at High Risk of Recurrence

by BRITTANY LOVELY and COURTNEY MARABELLA

ADJUVANT ATEZOLIZUMAB (TECENTRIQ) OUTPERFORMED best supportive care according to results from the phase 3 IMpower010 trial (NCT02486718), which supported FDA approval of the agent for patients with stage II to IIIA non-small cell lung cancer (NSCLC) with PD-L1 expression on at least 1% of tumor cells following resection and platinum-based chemotherapy.1

Investigator-assessed disease-free survival (DFS) served as the major efficacy outcome for the decision. The median DFS was not reached (95% CI, 36.1-not estimable [NE]) in the atezolizumab arm (n = 248) compared with 35.3 months (95% CI, 29.0-NE) in the best supportive care arm (n = 228; HR, 0.66; 95% CI, 0.50-0.88; P = .004).2 Exploratory analysis of overall survival in this population demonstrated an HR of 0.77 (95% CI, 0.51-1.17). A prespecified secondary subgroup analysis demonstrated a 57% reduction in the risk of progression or death in patients who received atezolizumab vs best supportive care in patients with PD-L1 expression on at least 50% of tumor cells (HR, 0.43; 95% CI, 0.27-0.68). The median DFS was not reached (95% CI, 42.3-NE) vs 35.7 months (95% CI, 29.7-NE), respectively.

In an interview OncologyLive®, Nasser Khaled Altorki, MD, provided insight on the results of the IMpower010 trial as well as post hoc analyses from the trial and what they signal for the remainder of this patient population. Altorki is a professor of cardiothoracic surgery and director of the Division of Thoracic Surgery at NewYork-Presbyterian Weill Cornell Medical Center in New York.

Q Please discuss the rationale for the IMpower010 trial.
Disease relapse and survival are an issue for patients with unresectable NSCLC and for patients with [stage] IB to IIIB disease. You can estimate recurrence rates to be anywhere [from] 40% to 70%. [Thus far, results from] randomized trials with adjuvant chemotherapy showed a 5% improvement in survival with [aromatase inhibitor]-driven chemotherapy. There haven’t been any big advances in that space [except for] of the ADAURA trial [NCT02511106], which randomized patients with EGFR-mutant NSCLC to osimertinib [Tagrisso] vs placebo.

There was a significant improvement [observed in patient populations from] North America and in Europe [but this is a small segment of the] [total patient] population; there haven’t been any big breakthroughs. There [have been] many attempts [to develop] vaccines and therapies targeting VEGF; none of those have worked.

[With IMpower010] we expected we would see dramatic improvements in survival in patients with advanced disease, like we [have] in the first line [setting] with the immune checkpoint inhibition; we [hypothesized] that these data would be reproduced in early-stage disease. There are several adjuvant trials using various immune checkpoints inhibitors in the adjuvant setting, and IMpower010 is the first to complete accrual and report on this primary end point.

Q What are the key takeaways from the analyses of IMpower010?
The difference in survival was significant. The hazard ratio was 0.66 with a very significant P value and this is the first study that shows a meaningful improvement in DFS.

We also looked at how [multiple] variables affected DFS in the cohort of patients, including disease stage, nodal status, extent of surgical resection, [number of prior] treatments, and types of chemotherapy delivered. In the post hoc unplanned exploratory analysis of the [effect] of these variables on DFS, what we found was heartening—these variables were balanced between the best-supportive-care arm and the atezolizumab arm. All of these variables seem to favor the atezolizumab arm, which has a significant improvement in DFS.

We repeated the exact post hoc analysis again [for those with] stage II to IIIA [disease] independent of PD-L1 expression. And again, DFS was better across the board in the atezolizumab arm, regardless of the type of therapy delivered, the [median] number of prior therapies, disease stage, etc. And finally, when in the intention-to-treat population, you recapitulate the initial finding, which is the DFS seems to favor the atezolizumab arm; [but] in this larger cohort, the significance boundary for DFS is not being crossed.

What is the value of all that? It’s important because [atezolizumab] is another tool that we can use in a population of patients at higher risk of disease recurrence.

Q Please expand on the importance of PD-L1 expression in this population.
PD-L1 is an important biomarker to look for in [patients with] early-stage disease. We do that routinely in patients with advanced disease, but it is not a matter of routine clinical practice for patients with early-stage disease. And I think the argument here is that it should occur because [PD-L1 expression] can be one variable that would influence how patients can be treated in the adjuvant setting.

Q Are there any adverse effects [AEs] clinicians should be aware of?
There’s been some discussion about the rate of AEs, but there were no AEs noted [in IMpower010] beyond what you would expect with immune checkpoint monotherapy or the [AEs] with atezolizumab monotherapy. In all cases we balance the risk of harm against the potential benefit of the drug in patients who have a high risk of disease or recurrence. That’s always a conversation that must happen between the patient and the physician. [Decisions are] also influenced by the patient’s age, comorbidities, performance status, etc.

REFERENCES
**PIVOTAL CLINICAL TRIAL**

**IMpower010 (NCT02486718)** is a multicenter, randomized, open-label trial that evaluated atezolizumab as a 1200-mg intravenous infusion every 3 weeks for 16 cycles vs best supportive care for the adjuvant treatment of patients with stage II to IIIA NSCLC who had complete tumor resection and were eligible to receive cisplatin-based adjuvant chemotherapy.

**BASELINE PATIENT CHARACTERISTICS**

- **Median age, years (range)**
  - Atezolizumab: 61 (34-82)
  - Best supportive care: 62 (26-84)

- **Disease stage**
  - Atezolizumab: 47.2% II A, 18.5% II B, 34.3% II A B
  - Best supportive care: 50.4% II A, 16.2% II B, 33.3% II A B

- **EGFR-mutation/ALK-rearrangement status**
  - Atezolizumab: 9.3% EGFR+, 4.8% ALK+, 86.9% EGFR−, 90.6% ALK−
  - Best supportive care: 49.6% EGFR+, 53.6% ALK+, 40.4% EGFR−, 46.4% ALK−

**EFFICACY RESULTS IN THE IMpower010 TRIAL**

- **PD-L1 ≥ 1% (n = 476)**
  - Outcome: Median DFS, months (95% CI)
    - Atezolizumab: 36.1 (30.0-NE)
    - Best supportive care: 35.3 (29.0-NE)

- **PD-L1 ≥ 50% (n = 229)**
  - Outcome: Median DFS, months (95% CI)
    - Atezolizumab: 42.3 (37.8-NE)
    - Best supportive care: 35.7 (29.7-NE)

- **PD-L1 1%-49% (n = 247)**
  - Outcome: Median DFS, months (95% CI)
    - Atezolizumab: 29.4 (25.0-NE)
    - Best supportive care: 24.0 (18.0-NE)

**WARNINGS AND PRECAUTIONS**

- Immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeneic hematopoietic stem cell transplantation after PD-1/PD-L1 inhibitors
- Embryo-fetal toxicity

**COMMONLY REPORTED ADVERSE EVENTS IN THE PRIMA STUDY**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Atezolizumab (N = 495)</th>
<th>Best supportive care (N = 495)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Rash</td>
<td>17%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cough</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

*In the intention-to-treat population.

**REFERENCES**

ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status\(^1-4\)

**Indication**

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

**Important Safety Information**

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

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

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

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

*Embryo-fetal toxicity and lactation:* Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.
YOU RESPOND WITH ZEJULA

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS

OVERALL POPULATION (N=733)

- Reduction in the risk of progression or death
- MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO
  (HR, 0.62; 95% CI, 0.50-0.76) P<0.0001

HRd POPULATION (n=373)

- Reduction in the risk of progression or death
- MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO
  (HR, 0.43; 95% CI, 0.31-0.59) P<0.0001

Study Design: PRIMA, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to first-line platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

Important Safety Information (continued)

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

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

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

Visit ZEJULAHCP.COM to explore the PRIMA data

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were reported in 28%, 27%, and 13%, respectively, of patients. Thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered ZEJULA with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients. Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the dose of ZEJULA, if necessary [see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information].

5.4 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports [see Adverse Reactions (6.2)]. Signs and symptoms of PRES include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. Monitor all patients treated with ZEJULA for signs and symptoms of PRES. If PRES is suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinstituting ZEJULA in patients previously experiencing PRES is not known.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) of full prescribing information]. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets active dividing cells in animals and patients (e.g., bone marrow) [see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 5 months after the last dose of ZEJULA [see Use in Specific Populations (8.1, 8.3)].

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

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

6 ADVERSE REACTIONS

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

- Myelodysplastic Syndrome/Acute Myeloid Leukemia
- Neutropenia
- Leukopenia
- Cough
- Insomnia
- Gastrointestinal disorders
- Fatigue
- Investigations
- Metabolism and nutrition disorders
- Psychiatric disorders
- Renal and urinary disorders
- Vascular disorders

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reactions of all grades in >10% of 1,314 patients who received ZEJULA in the pooled PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (52%), constipation (39%), musculoskeletal pain (33%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leucopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (10%), dysgeusia (14%), acute kidney injury (13%), urinary tract infection (2%), and hypernatremia (1%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.3 to 29 months). All Patients Receiving ZEJULA in PRIMA

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

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in <1% of patients who received ZEJULA included thrombocytopenia (7.7%), anemia (1.5%), and nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

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

Table 1: Adverse Reactions Reported in ≥2% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
<th>Placebo Grades 1-4</th>
<th>Placebo Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=86)</td>
<td>484</td>
<td>86</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (n=367)</td>
<td>86</td>
<td>484</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Blood and lymphoid system disorders

- Thrombocytopenia 66 3 39 0.4
- Anemia 64 18 31 2
- Neutropeniaa 42 8 21 1
- Leukopeniaa 28 9 5 0.4

Gastrointestinal disorders

- Nausea 57 28 1 1
- Constipation 40 20 1 0.4
- Vomiting 22 12 1 1

General disorders and administration site conditions

- Fatigue 51 41 3 1

Investigations

- AST/ALT elevation 14 7 3 0.8

Metabolism and nutrition disorders

- Decreased appetite 19 8 1 0
- Musculoskeletal and connective tissue disorders
  - Musculoskeletal pain 39 38 1 0
  - Nervous system disorders
    - Headache 26 15 0.4 0
    - Dizziness 19 13 0 0.4

Psychiatric disorders

- Insomnia 25 15 1 0.4

Renal and urinary disorders

- Acute kidney injury 12 5 0.2 0

Respiratory, thoracic and mediastinal disorders

- Dyspnea 22 13 0.4 1
- Cough 18 15 0 0.4

Vascular disorders

- Hypertension 18 7 6 1

AST/ALT = Aspartate transaminase/Alanine aminotransferase

*Adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.

†Common Terminology Criteria for Adverse Events version 4.02.
Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA. Among patients who received ZEJULA with the dose based on weight or platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in ≥2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in ≥2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%). Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA.

*Common Terminology Criteria for Adverse Events version 4.02.
Includes neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.
Includes leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.
Includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatinine increased.

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>87/66/29</td>
<td>1</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74/13/37</td>
<td>0</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71/38/9</td>
<td>0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66/57/3</td>
<td>3</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66/25/23</td>
<td>1</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51/29/7</td>
<td>3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46/21/1</td>
<td>0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40/23/0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36/34/1</td>
<td>0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35/17/1</td>
<td>0.4</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29/17/2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>54/5/21</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>50/28/23</td>
<td>1</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>36/8/15</td>
<td>1</td>
</tr>
<tr>
<td>Leukopeniaa</td>
<td>28/11/5</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53/21/1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>31/15/1</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17/9/0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48/36/3</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19/5/1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22/12/1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14/13/0</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21/14/0</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>21/14/0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18/10/0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17/9/5</td>
<td>2</td>
</tr>
</tbody>
</table>

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81/70/21</td>
<td>0</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>70/36/6</td>
<td>0</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>63/15/18</td>
<td>0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63/56/2</td>
<td>1</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>60/27/15</td>
<td>0</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52/30/5</td>
<td>4</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43/17/1</td>
<td>0</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44/30/0</td>
<td>0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41/22/0</td>
<td>0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31/19/1</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28/15/2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>61/5/29</td>
<td>0.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>50/7/25</td>
<td>0</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>30/6/20</td>
<td>2</td>
</tr>
<tr>
<td>Leukopeniaa</td>
<td>17/8/5</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>74/35/3</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>40/20/8</td>
<td>0.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34/16/2</td>
<td>0.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20/6/5</td>
<td>0.0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18/12/0</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10/4/0.3</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>57/41/8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>61/5/29</td>
<td>0.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>50/7/25</td>
<td>0</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>30/6/20</td>
<td>2</td>
</tr>
<tr>
<td>Leukopeniaa</td>
<td>17/8/5</td>
<td>0</td>
</tr>
</tbody>
</table>

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

### Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%), anemia (20%), and neutropenia (15%). The common discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>61/5/29</td>
<td>0.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>50/7/25</td>
<td>0</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>30/6/20</td>
<td>2</td>
</tr>
<tr>
<td>Leukopeniaa</td>
<td>17/8/5</td>
<td>0</td>
</tr>
</tbody>
</table>

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

### Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in ≥3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.
Thrombocytopenia includes events with preferred terms of common Terminology Criteria for Adverse Events version 4.02. AST/ALT=Aspartate transaminase/alanine aminotransferase.

Table 8: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4 (n=463)</th>
<th>Grades 3-4 (n=463)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83 (26)</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66 (28)</td>
<td>5</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60 (28)</td>
<td>28</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57 (18)</td>
<td>15</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53 (9)</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40 (4)</td>
<td></td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40 (8)</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34 (6)</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34 (15)</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>29 (2)</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27 (2)</td>
<td></td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders: Pancytopenia.


8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women. See Clinical Pharmacology (12.1) of full prescribing information. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryofetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In FDA/NCI, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. In NOVA, 35% of patients were aged 65 years or older and 8% were aged 75 years or older. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater incidence of some older individuals cannot be ruled out.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily (see Dosage and Administration (2.4) of full prescribing information). Niraparib exposure increased in patients with moderate hepatic impairment.

17 PATIENT COUNSELING INFORMATION

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

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

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

Posterior Reversible Encephalopathy Syndrome

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

Dosing Instructions

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

Embryo-Fetal Toxicity

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

Contraception

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

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose (see Use in Specific Populations (8.3)).

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

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

ZIC:1BRS 03/2021

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Produced in USA.
Therapeutic Frontiers Expand for Patients With Relapsed/Refractory Multiple Myeloma

by SHAMBAVI RICHARD, MD

MULTIPLE MYELOMA IS A CLONAL plasma cell neoplasm characterized by bone lesions, renal impairment, cytopenias, and immunodeficiency. Despite significant therapeutic advancements in the past 2 decades that have resulted in improved survival, myeloma remains an incurable disease. The immune environment in which the cancer cells thrive is known to be a key player in the evolution of monoclonal gammapathies from premalignant stages to advanced malignancy. Further, immune dysregulation—marked by T-cell exhaustion, tolerance induction by tumor microenvironment, and tumor escape from immune surveillance—is important in the pathogenesis. Therefore, various immune strategies have been developed, including immune-enhancing drugs such as immunomodulatory drugs, checkpoint inhibitors, monoclonal antibodies, and, more recently, chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies for T-cell redirection.

ENGINEERING THE FUTURE OF MULTIPLE MYELOMA TREATMENT

CAR T cells are T lymphocytes genetically modified by viral vectors or nonviral technology such as DNA transposons to express a synthetic receptor to target a specific antigen. The single chain variable fragment (ScFv) on the ectodomain of the CAR recognizes tumor-associated antigens on the surface of tumor cells, binds to them, and initiates a cascade of cytotoxic signaling that leads to tumor lysis.

The ectodomain is linked to the intracellular domains by a hinge/transmembrane region, commonly derived from CD8 or IgG4. The intracellular portion is the signaling domain. In the first generation of CARs, this included only the CD3ζ signaling domain, which lacked a proliferation profile. Second- and third-generation CARs now include 1 (second generation) or 2 (third generation) costimulatory domains that are typically 4-1BB, CD28, and/or OX-40 to promote efficient T-cell signaling and persistence. Fourth-generation CARs, which further affect the tumor microenvironment to induce cytokine production after the CAR recognizes the target antigens, and fifth-generation CARs are being developed to further improve CAR efficiency and longevity.

On the other hand, bispecific antibodies use patients’ unengineered T cells. The off-the-shelf antibody is designed so that 1 end binds to a multiple myeloma cell and the other end binds to a killer T cell. The first bispecific antibody for multiple myeloma was developed with an ScFv that attached to the tumor antigen and another that attached to CD3 of the T-cell receptor complex of the T cell with a linker. The half-life was short, and continuous infusion was required. Since then, bispecific antibodies are manufactured with an Fc segment that increases the half-life so that the agent can be administered weekly or less frequently; this is the treatment of choice in ongoing clinical trials. New agents in development include trispecific antibodies that may have a costimulatory protein or target dual myeloma antigens or antibodies that engage natural killer cells.

There are several tumor antigens being investigated as suitable targets for CAR T-cell and T-cell redirected therapies, such as CD38, CD138, SLAMF7, CD19, and more. However, the most widely studied target for both CAR T-cell therapy and bispecific antibody therapies is B-cell maturation antigen (BCMA).

BCMA is a cell surface receptor in the tumor necrosis factor receptor superfamily member 17. It is deemed an ideal antigenic target because it is expressed specifically on normal and malignant plasma cells but not on hematopoietic stem cells, and it has higher expression on myeloma cells than normal plasma cells. It plays a key role in B-cell maturation and differentiation and promotes myeloma cell growth by binding to its ligands BAFF and APRIL. Expression of BCMA increases with progression from monoclonal gammopathy of undetermined significance to advanced myeloma.

TARGETING BCMA

Based on encouraging results from the first major global multicenter phase 1 anti-BCMA CAR T study (NCT02658929) conducted in relapsed or refractory multiple myeloma, investigators initiated the pivotal phase 2 KarMMa trial (NCT03361748). The results of this trial were updated at the 18th International Myeloma Workshop (IMW), held in Vienna, Austria, in September 2021. Idecabtagene vicleucel (ide-cel; Abecma), formally bb2121, is an anti-BCMA second-generation CAR...
construct with 41BB costimulatory domain. Among 128 patients enrolled in the KarMMA study, 84% were triple-class refractory. At a median follow-up of 24.8 months, overall response rate (ORR) was 73%, with complete response (CR) or stringent CR (sCR) reported in 33% of patients. Minimal residual disease (MRD) was negative in 79% of complete responders. Further, responses were attained at a median of 1 month (range, 0.5-8.8) and the median duration of response (DOR) was 10.9 months.

The median progression-free survival (PFS) was 8.6 months and median overall survival (OS) was 24.8 months. DOR and PFS were improved in the higher-dose ranges and in complete responders. Similar degrees of responses were observed in all subgroups, including Revised International Staging System for multiple myeloma III criteria, extramedullary disease, and high tumor burden. In terms of adverse events (AEs), cytopenias were observed in 97% of patients. Grade 3/4 neutropenia was seen in 89% of patients, grade 3/4 thrombocytopenia was seen in 52%, and grade 3/4 infections in 23%. Cytokine release syndrome (CRS) was seen in 84% of patients: 78% at grade 1/2, 6% at grade 3 or higher. CRS occurred at a median onset of 2 days and median duration was 5 days. Neurotoxicity was reported in 18% of patients, 4% of whom reported the AE as grade 3 or higher. Results of the study led to FDA approval of the first commercially approved CAR T-cell product in March 2021.

CARTITUDE-1 was a phase I/II study (NCT03548207) that used a different CAR T product, ciltacabtagene autoleucel (cilta-cel). Updated findings were presented from Usmani et al9 at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting and at the IMW from Jagannath et al.8 Cilta-cel is a lentiviral vector-based anti-BCMA construct with a 4-1BB costimulatory domain. The BCMA-catching domain targets 2 different epitopes simultaneously, increasing the binding affinity, and is the same CAR construct as in the Chinese trial LEGEND-2 (NCT03090659).

In CARTITUDE-1, 97 patients with a median of 6 prior lines of therapy were enrolled. At baseline, 88% were triple-class refractory and 99% refractory to last line of therapy. At a median follow-up of 18 months, the ORR was 98% for all patients and included an sCR rate of 80%. Responses were attained at a median of 1 month and deepened over time. The median DOR was 21.8 months overall (95% CI, 21.8-not estimable) and was not reached in patients with sCR. MRD negativity was achieved in 92.0% of evaluable patients.

The 18-month PFS rate was 66% (95% CI, 54.9%-75.0%) and the 18-month OS rate was 80.9% (95% CI, 71.4%-87.6%). These results far surpass outcomes with other non-T-cell mediated novel agent therapies in triple-class refractory patients.

In terms of safety, cytopenias were universal and 92 of 97 patients experienced any-grade CRS; 95% were grade 1/2 and had a median time of onset of 7 days and duration of 4 days. All-grade neurotoxicity was reported for 21% of patients, 10% of whom had neurotoxicity of grade 3 or higher. Although most neurotoxic events occurred in the setting of CRS, 12 patients had late neurotoxicity, 6 of whom resolved, 1 had ongoing neurotoxicity, and 1 died because of neurotoxicity. There were 21 deaths on study: 2 occurred in fewer than 100 days, 10 deaths were because of disease progression, and 6 were because of treatment-related AEs. Late recovery (greater than 1 month) of grade 3/4 cytopenias from first onset was seen in 10% of neutropenia and 26% of thrombocytopenia. Cilta-cel is expected to gain FDA approval this year.

“With the arrival of this new era of powerful immunotherapeutic tool such as CAR T-cell therapy and T-cell redirective agents, a sound understanding of their optimal use is key to maximizing their potential.”

—SHAMBAVI RICHARD, MD

COMPARING OUTCOMES

At the American Society of Hematology (ASH) Annual Meeting 2020, Shah et al7 presented an analysis that compared efficacy outcomes seen in the KarMMA trial with those reported from the MAMMOTH study, which was a retrospective observational study of conventional care regimens in patients with triple-class refractory multiple myeloma.

The MAMMOTH study, which has been used in other comparative studies, has been a benchmark for investigators to compare therapeutic maneuvers in patients with triple-class exposed relapsed or refractory multiple myeloma who have received various standard-of-care therapies. The analysis applied matching-adjusted indirect comparisons to assess the efficacy of ide-cel and conventional care and showed that, in a matched population, ide-cel treatment was associated with a significantly higher ORR, PFS, and OS than conventional care.

Cilta-cel was similarly compared with conventional treatment in the MAMMOTH study and was presented by Costa et al at ASCO 2021.9 The MAMMOTH data set was used to identify patients with multiple myeloma refractory to anti-CD38 monoclonal antibodies who would meet eligibility for CARTITUDE-1 and who received conventional therapy. The intention-to-treat population (ITT) in CARTITUDE-1 was defined as patients who underwent apheresis, and a modified ITT population was defined as
subset of patients who received cilta-cel at the recommended phase 2 dose (RP2D).

ORR, PFS, and OS for both the ITT population and modified ITT population in CARTITUDE-1 vs matching MAMMOTH cohorts were found to be superior. Specifically, the ORR in the ITT cohort was higher in CARTITUDE-1 compared with the MAMMOTH counterpart (84% vs 28%). Patients in the CARTITUDE-1 ITT cohort vs MAMMOTH cohort had improved PFS and OS rates at 12 months, 73% vs 12% and 83% vs 39%, respectively. Comparing the modified ITT cohorts, patients in CARTITUDE-1 had superior ORR (96% vs 30%), 12-month PFS rate (79% vs 15%), and 12-month OS rate (88% vs 41%).

Therefore, in patients with relapsed or refractory multiple myeloma beyond therapy with immunomodulatory drugs, proteasome inhibitor, and anti-CD38 monoclonal antibody, treatment with CAR T, ide-cel, or cilta-cel is associated with higher response rate and superior PFS and OS when compared with conventional treatment.

Other CAR T trials were reported at ASH 2020 and are being studied in various phase 1/2 trials. Research is directed at improving the efficacy and persistence of CAR products, which vary by source of product (autologous vs allogeneic CAR T cells), choice of vector (lentiviral, retroviral, or nonviral DNA transposon technology), use of humanized ScFv to prevent immunogenicity, CD4/CD8 ratio controlled to enrich for central memory phenotype to improve longevity of CAR T cells, dual target constructs to prevent relapses because of antigen escape, CARs against non-BCMA targets to treat BCMA negative relapses, and more.

Bispecific antibodies are in earlier stages of development than CAR T. The majority of antibodies target BCMA, although there are some targeting antigens other than BCMA that have great potential in patients who have relapsed post BCMA-targeted therapies with BCMA-negative plasma cells.

Teclistamab is an anti-BCMA/anti-CD3 bispecific antibody with intravenous and subcutaneous formulations. Results of the MajesteC-1 study (NCT03145181) were published in Lancet.10,11 Investigators treated 157 patients with median of 6 prior lines of therapy, of whom 82% were triple-class refractory, 90% were refractory to last regimen, and 85% were previously transplanted were enrolled in a dose escalation/expansion study. A total of 40 patients received the RP2D of 1500 μg/kg. At RP2D, the median time to response was 1 month and median time to CR was 3 months.

At a median follow-up of 7.2 months, median DOR was not reached (7.2-not reached). The ORR was 65% in the RP2D group, 58% had a very good partial response (VGPR) or better, and 40% had a CR or better. Importantly, the majority of patients in CR were MRD-negative at 10⁻⁶.

Among responders, 85% were alive and progression-free at follow-up. The most common AEs of any grade were CRS, all grade 1 or 2, (70%) and neutropenia (65%). Grade 3 or 4 AEs occurred in 80% of patients, with the most common being neutropenia (40%), anemia (28%), and thrombocytopenia (20%). Infections occurred in 45% of patients and were grade 3 or higher in 23%.

Talquetamab is an anti-GPRC5D/CD3 first-in-class duo antibody. Results from the phase 1 MonumenTAL-1 trial (NCT04634552) were presented by Chari et al at ASH 202012 and updated at the IMW by van de Donk et al.13 GPRC is highly expressed in poor-risk myeloma, and in hair follicles. In the MonumenTAL-1 trial, 174 patients with a median of 6 prior lines of therapy were enrolled, 102 to the intravenous arm and 72 to the subcutaneous formulation arm, in dose escalation and expansion cohorts. At baseline 71% of patients were triple-class refractory and 86% were refractory to last line of therapy; 21% of patients had received prior BCMA-targeted therapies.

The ORR was 70% at the RP2D, and 50% of responders had a VGPR or better, with a median time to first confirmed response of 1 month. Responses were durable and deepened over time, with 81% of responders continuing on treatment after a median follow-up of 6.3 months. CRS was reported in 79% of patients; 4% had CRS of grade 3/4. Median time to onset of CRS was a day after subcutaneous dose, and the duration was 2 days. Neurotoxicity was reported in 7% of patients (grade 1/2) and was mostly in the context of CRS. Grade 1/2 skin-related AEs were seen in 75% of patients and nail-related AEs in 18%. Dysgeusia was reported in 57% of patients. A phase 2 expansion study of talquetamab in the RP2D MonumenTAL-2 is recruiting.

Ongoing Research in Bispecific Antibodies

Various other bispecific antibodies are in clinical trials, including Regeneron 5458, another anti-BCMA/anti-CD3 bispecific antibody with very encouraging results reported at ASH last year.14 The ORR was 63% and responses were achieved by 1 month. The median DOR was 6 months, and among responders with more than 6 months of follow-up, 83% had ongoing responses for up to 13 months and 74% of responders remained on treatment.

TNB-383B is a fully human triple-chain BCMA × CD3 bispecific antibody with a unique anti-CD3 moiety for target lysis with minimal cytokine release and 2 anti-BCMA moieties. It is administered intravenously every 3 weeks without step-up dosing. Data for 58 patients from the ongoing first-in-human study were presented at ASH 2020.15 Safety data were comparable with results of other studies.

Cevostamab is another non-BCMA bispecific antibody. The target antigen is FcRH5, which is found on naïve and memory B cells and plasma cells. The anti-FcRH5/anti-CD3 is administered intravenously every 3 weeks, and data were presented at ASH 2020.16 Finally, CC-93269, a bispecific antibody with 1 CD3 and 2 BCMA binding sites, shows encouraging early data as well.

Future directions for bispecific antibodies include understanding resistance mechanisms, studying them in combination with various agents, and understanding sequencing strategies. Because myeloma is marked by clonal heterogeneity, combinations of drugs with different mechanisms of action and nonoverlapping toxicities are frequently used with success. With the arrival of this new era of powerful immunotherapeutic tools such as CAR T-cell therapy and T-cell redirective agents, a sound understanding of their optimal use is key to maximizing their potential.
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system event; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

**Infections:** Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jiroveci* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

**Cytopenias:** In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.

**Cardiac Arrhythmias and Cardiac Failure:** Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

**Hypertension:** Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
LIVING LONGER WITHOUT PROGRESSION
Superior PFS: IMBRUVICA® + rituximab vs FCR in E1912

89% (95% CI: 85, 92) estimated PFS rate with IMBRUVICA® + rituximab at 3 years vs 70% (95% CI: 61, 78) with FCR in patients ≤70 years old

HR=0.34 (95% CI: 0.22, 0.52; P<0.0001) (primary endpoint)

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).

1L=frontline, CI=confidence interval, FCR=fludarabine, cyclophosphamide, and rituximab,
HR=hazard ratio, PFS=progression-free survival.

Visit IMBRUVICAHCP.com to learn more

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS
The most common adverse reactions (>30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (38.5%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions (>5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions.

Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS
CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS
Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib)

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 20- to 25-times higher than those reported in patients with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. [See Use in Specific Populations].

ADVERSE REACTIONS

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

- Hemorrhage [see Warnings and Precautions]
- Infections [see Warnings and Precautions]
- Cytopenias [see Warnings and Precautions]
- Cardiac Arrhythmias and Cardiac Failure [see Warnings and Precautions]
- Hypertension [see Warnings and Precautions]
- Second Primary Malignancies [see Warnings and Precautions]
- Tumor Lysis Syndrome [see Warnings and Precautions]

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

The data in the WARNINGS AND PRECAUTIONS reflects exposure to IMBRUVICA in 6 trials as a single agent at 420 mg orally once daily in 475 patients and at 560 mg orally once daily in 174 patients and in 4 trials administered in combination with other drugs at 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies who received IMBRUVICA, 87% were exposed for 6 months or longer and 68% were exposed for greater than one year. In this pooled safety population of 1,476 patients with B-cell malignancies, the most common adverse reactions (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure to IMBRUVICA in one single-arm, open-label clinical trial (Study 1102) and five randomized controlled clinical trials (RESONATE, RESONATE-2, HELIOS, ILLUMINATE, and E1912) in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with untreated or prior treatment-refractory disease.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 22% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

CARDIAC ARRHYTHMIAS AND CARDIAC FAILURE: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias [see Adverse Reactions].

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop new or worsening symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Dosage and Administration (2.2) in Full Prescribing Information].

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

SECONDARY MALIGNANCIES: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA in clinical trials. The most frequent secondary primary malignancy was non-melanoma skin cancer (6%).

ADVERSE REACTIONS

The following adverse reactions were reported with IMBRUVICA treatment and were more frequent than with placebo:

Cardiac arrhythmias and cardiac failure:
- In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater hypertension occurred in 8% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding [see Clinical Studies (14) in Full Prescribing Information].

Infections:
- Fatal and serious infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,478 patients who received IMBRUVICA in clinical trials [see Adverse Reactions].

Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias:
- In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 22% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

The most common adverse reactions in patients with CLL/SLL (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA. Major hemorrhage: Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage (including subdural hematoma), gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively.

The most frequent secondary primary malignancy was non-melanoma skin cancer (6%).

IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

CONTRAINDICATIONS

None
Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td>Second malignancies</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Percent of Patients (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>43</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal pain</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>13</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Cough</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Pneumonia*</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>10</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>11</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Contusion</td>
<td>11</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
<td>10</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

**RESOLUTE** Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 11 months in RESOLUTE-2.
Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 4</td>
<td>17 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 1</td>
<td>39 1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 1</td>
<td>16 0</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>14 1</td>
<td>4 1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 0</td>
<td>20 1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 3</td>
<td>11 1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11 0</td>
<td>2 0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>36 4</td>
<td>20 0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16 1</td>
<td>7 1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11 0</td>
<td>5 0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>22 0</td>
<td>15 0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 1</td>
<td>10 0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>21 4</td>
<td>12 2</td>
</tr>
<tr>
<td>Bruising*</td>
<td>19 0</td>
<td>7 0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>17 0</td>
<td>5 0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13 0</td>
<td>6 0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>13 0</td>
<td>8 0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 0</td>
<td>2 0</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>15 2</td>
<td>3 1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14 8</td>
<td>7 4</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10 1</td>
<td>8 1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>14 4</td>
<td>1 0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 1</td>
<td>10 2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 0</td>
<td>12 1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10 0</td>
<td>12 0</td>
</tr>
</tbody>
</table>

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>55 28</td>
<td>67 31</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>47 7</td>
<td>58 14</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36 0</td>
<td>39 2</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term. The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Table 7: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + BR (N=287)</th>
<th>Placebo + BR (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>66 61</td>
<td>60 56†</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34 16</td>
<td>26 16</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 2</td>
<td>23 1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 1</td>
<td>8 1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>32 4</td>
<td>25 1</td>
</tr>
<tr>
<td>Bruising*</td>
<td>20 &lt;1</td>
<td>8 &lt;1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>29 2</td>
<td>20 0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12 &lt;1</td>
<td>5 0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25 4</td>
<td>22 2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>19 2†</td>
<td>9 1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>11 5</td>
<td>5 2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13 2</td>
<td>10 3</td>
</tr>
<tr>
<td>Skin infection†</td>
<td>10 3</td>
<td>6 2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10 2</td>
<td>6 0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

*† Includes multiple ADR terms

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48 39</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36 19</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>36 3</td>
</tr>
<tr>
<td>Bruising*</td>
<td>32 3</td>
</tr>
</tbody>
</table>
**IMBRUVICA® (ibrutinib)**

### Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in ILLUminate (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>33</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>13</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>25</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>17</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms
† Includes one event with a fatal outcome.

**E1912: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.**

### Table 9: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912 (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>80</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 10: Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43</td>
<td>7</td>
<td>69</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>30</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>AST increased</td>
<td>25</td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria.
Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular tachycardias (ventricular extrastoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 8.4% versus 1.6% and for Grade 3 or greater was 4.0% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) was estimated to be 0.4% and Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarhoea: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and for 958 patients in the control arm), diarhoea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarhoea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarhoea compared with 0% in the control arm.

Based on data from 1,605 of these patients, the median time to first onset was 1 day (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarhoea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarhoea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarhoea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarhoea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 58) for Grade 3 diarhoea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3).

Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 617) versus 105 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analyzed. The median treatment duration was 51 months (range, 0 to 98 months) for CLL/SLL, 11 months (range, 0 to 97 months) for MCL, and 47 months (range, 0 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall rate of hypertension was 5%.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of IMBRUVICA. 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.

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis, ascites, liver failure
- Gastrointestinal disorders: intestinal intussusception
- Metabolic and nutrition disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), Stevens-Johnson Syndrome Toxic Epidermal Necrolysis, Hair Loss
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

IMBRUVICA® (ibrutinib)
Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

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

- Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].

- Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].

- Cardiac arrhythmias and cardiac failure: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema [see Warnings and Precautions].

- Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].

- Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].

- Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].

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

Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations].

Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations, Nonclinical Toxicology (13.1) in Full Prescribing Information].

- Lactation: Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose [see Use in Specific Populations].

- Inform patients to take IMBRUVICA orally once daily according to their physician’s instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].

Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

- Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].

- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

Active ingredient made in China.

Distributed and Marketed by: Pharmacyclics LLC Sunnyvale, CA USA 94085 and Marketed by: Janssen Biotech, Inc. Horsham, PA USA 19044

Patent http://www.imbruvica.com
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Adaptation Is Key to Advancing Care for Adult Patients With Leukemia

by ANDREW D. SMITH

IT WOULD BE DIFFICULT to look at data involving practice-changing agents for patients with leukemia and miss the name Jorge E. Cortes, MD. An investigative leader for nearly 30 years, Cortes has led the development of numerous leukemia treatments, including trials for the second-generation tyrosine kinase inhibitor (TKI) bosutinib (Bosulif), which is widely used for chronic myeloid leukemia (CML); omacetaxine mepe-succinate (Synribo), a drug approved for patients with CML when TKIs have stopped working; the third-generation TKI ponatinib (Iclusig), another CML treatment; and glasdegib (Daurismo), a smoothened inhibitor approved for the treatment of older patients with acute myeloid leukemia (AML) and complications like heart or kidney disease that preclude use of intensive induction chemotherapy.

Today, Cortes is leading something even larger than drug trials: the Georgia Cancer Center at Augusta University, which named him its director in 2019, following a 20-plus year career at The University of Texas MD Anderson Cancer Center in Houston. Working to make Georgia Cancer Center a world-class facility and continuing with as much research as possible keeps Cortes busy, but he has still found time to cochair the 26th Annual International Congress on Hematologic Malignancies® hosted by Physicians’ Education Resource® (PER®), LLC.

The hybrid interactive conference will be held from Thursday, February 24, 2022, to Sunday, February 27, 2022, at the Eden Roc in Miami Beach, Florida. The 4-day event will focus on leukemias, lymphoma, and myeloma. Its presentations and panels will cover the latest developments in chimeric antigen receptor (CAR) T-cell therapy, the most pivotal new trial results, the use of genomics and molecular testing in hematological cancers, and how to cope with the emerging value based-care landscape.

At MD Anderson—where he rose from a fellow to the deputy chair of the Department of Leukemia—Cortes established himself as one the world’s leading leukemia researchers and the coauthor of more than 1000 published papers. At Georgia Cancer Center, he has less time for research, but he has still managed to launch another multicenter trial of an experimental CML treatment. “[Cortes] is truly a world expert on all things leukemia, has peerless clinical experience, and is an undisputed leader in the field. He has been instrumental in a very large number of trials that have led to drug approvals, and he ranks among the most published authors in the scientific world,” Alexander E. Perl, MD, MS, said.

Perl is an associate professor of medicine at Perelman School of Medicine at the University of Pennsylvania and a member of the leukemia program in the Abramson Cancer Center in Philadelphia, who has worked with Cortes on trials of FLT3 inhibitors.

“He’s an excellent speaker as well,” Perl added, “and will make a great chair for the conference.”

Courtney D. DiNardo, MD, MSCE, a clinical researcher in the Department of Leukemia at MD Anderson Cancer Center, said the key to Cortes’ success...
is a level of drive that is unusual even in a world of highly driven people. “He’s always moving; he’s always thinking. He’s kind of like the Energizer Bunny. He just keeps going and going,” she said.

The agenda for the International Congress on Hematologic Malignancies® features dozens of presentations and panels, and most of them are followed directly by question-and-answer sessions with thought leaders. The other program cochairs are Andre H. Goy, MD, physician in chief at Hackensack Meridian Health Oncology Care Transformation Service, chairman and chief physician officer at John Theurer Cancer Center, Lydia Pfund Chair for Lymphoma, Academic Chairman Oncology at Hackensack Meridian School of Medicine, and professor of medicine at Georgetown University in Hackensack, New Jersey, and Sagar Lonial, MD, FACP, chief officer of Winship Cancer Institute of Emory University in Atlanta, Georgia.

The key topics for discussion will include the following:

- current and emerging biomarkers to determine risk and choose therapy for patients with hematologic malignancies;
- key clinical data on current treatment approaches;
- recent clinical trial results on emerging therapeutic approaches; and
- approaches to mitigate and manage treatment-related adverse events.

**FIGURE. The Road to Approval: Results From Venetoclax Studies in AML**

<table>
<thead>
<tr>
<th>Accelerated approval: November 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPDATED RESULTS FROM PHASE 1 AND PHASE 1/2 TRIALS</strong></td>
</tr>
<tr>
<td><strong>M14-358 (NCT02203773):</strong> phase 1 nonrandomized, open-label trial of venetoclax in combination with azacitidine or decitabine in patients with newly diagnosed AML</td>
</tr>
<tr>
<td>Outcome</td>
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<tr>
<td>CR rate (95% CI)</td>
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<tr>
<td>Median duration of CR</td>
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<tr>
<td>CRh rate (95% CI)</td>
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<tr>
<td>Median duration of CR + CRh</td>
</tr>
</tbody>
</table>

| **M14-387 (NCT022287233):** phase 1/2 nonrandomized, open-label trial of venetoclax plus low-dose cytarabine in patients with newly diagnosed AML |
| Outcome | Venetoclax plus low-dose cytarabine (n = 61) |
| CR rate (95% CI) | 21% (12%-34%) |
| Median duration of CR | 22.9 months |
| CRh rate (95% CI) | 21% (12%-34%) |
| Median duration of CR + CRh | 14.3 months |

<table>
<thead>
<tr>
<th>Full approval: October 2021</th>
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<tbody>
<tr>
<td><strong>RESULTS FROM CONFIRMATORY PHASE 3 TRIALS</strong></td>
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<tr>
<td><strong>VIALE-A (NCT02993523):</strong> phase 3 randomized, double-blind, placebo-controlled, multicenter trial of venetoclax in combination with azacitidine vs placebo with azacitidine in patients with newly diagnosed AML</td>
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<tr>
<td>Outcome</td>
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<tr>
<td>Median OS, months (95% CI)</td>
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<tr>
<td>HR</td>
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<tr>
<td>CR rate (95% CI)</td>
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<tr>
<td>Median duration of CR</td>
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<tr>
<td>CR + CRh rate (95% CI)</td>
</tr>
<tr>
<td>Median duration of CR + CRh</td>
</tr>
</tbody>
</table>

| **VIALE-C (NCT03069352):** phase 3 randomized, double-blind, placebo-controlled, multicenter trial that evaluated venetoclax in combination with low-dose cytarabine vs placebo with low-dose cytarabine in patients with newly diagnosed AML |
| Outcome | Venetoclax plus low-dose cytarabine (n = 286) | Placebo plus low-dose cytarabine (n = 145) |
| CR rate (95% CI) | 27% (20%-35%) | 7.4% (2.4%-16%) |
| Median duration of CR | 11.0 months | 8.3 months |
| CR + CRh rate (95% CI) | 47% (39%-55%) | 15% (7.3%-25%) |
| Median duration of CR + CRh | 11.1 months | 6.2 months |
| Median OS, months (95% CI)* | 7.2 (5.6-10.1) | 4.1 (3.1-8.8) |
| HR | 0.75; 95% CI, 0.52-1.07; P = .114 |

AML, acute myeloid leukemia; CR, complete remission; CRh, complete remission with partial hematologic recovery; OS, overall survival.

*Did not significantly improve survival; approval was based on CR rate.

A MODERN LANDSCAPE

Cortes recently sat down for an in-depth interview with OncologyLive® to preview the conference and share his thoughts about the major trends in leukemia treatment.

“When I started, leukemia treatment was easy,” Cortes said. “[Individuals] with AML got 7 plus 3 [cytarabine continuously for 7 days and an anthracycline on each of the first 3 days of a treatment cycle]. Patients with CML would get interferon. And individuals with a model of proliferative neoplasms got hydroxyurea. And that was it. It was very easy. Unfortunately, the results were terrible.

“Nowadays, there’s a lot more complexity in our understanding of the biology. There’s not one AML, there’s not one ALL [acute lymphoblastic leukemia]. There are a lot more challenges in classifying the cancer, and the same is true in treatment. We have a lot more treatment options, but the increase in treatment options means that it’s a lot harder to pick the right one. How do I select when I have 3 or 4 options? How do I combine them? What is the relative value? The answers to all these questions are
evolving very rapidly because there [are] a lot of data coming out.”

Among the biggest topics of conversation at the hematology conference will be recent trial results for CAR T-cell therapy. In October, the FDA approved brexucabtagene autoleucel (Tecartus) for adults with relapsed or refractory B-cell precursor ALL. The approval was based on results from the ZUMA-3 trial (NCT02614066), in which 71 patients were enrolled and underwent leukapheresis. The CAR T-cell therapy was then successfully manufactured for 65 of those patients and administered to 55. At the median follow-up of 16.4 months, 31 (56%) patients reached complete remission (CR). The median duration of remission was 12.8 months (95% CI, 8.7 months-not estimable [NE]). Median relapse-free survival was 11.6 months (95% CI, 2.7-15.5), and median overall survival (OS) was 18.2 months (95% CI, 15.9 months-NE). Among responders, median OS was not reached at the time of analysis.1

Among responders, median OS was not reached at the time of analysis.1 A few days before that approval, Kite submitted a supplemental biologics license application to the FDA to expand the current indication of the CAR T-cell therapy axicabtagene ciloleucel (Yescarta) to include the second-line treatment of adult patients with relapsed or refractory large B-cell lymphoma. The application was based on findings from the phase 3 ZUMA-7 trial (NCT03391466), which showed improved event-free survival compared with standard of care after a median follow-up of 2 years. Among the 359 patients who were randomized 1:1 to CAR T-cell therapy or standard of care, patients in the experimental group experienced a 60% reduction in events.2

“We will present a lot of data on CAR T-cell therapy,” Cortes said. “This is a rapidly emerging field, with a large number of new trial results, not just in acute lymphoblastic leukemia but, increasingly, in other areas as well, and we dedicate a whole section of the conference to the understanding of CAR T-cells. This is something that was addressed last year, and we will do it again because new information keeps coming, and now there’s the new indication in acute lymphoblastic leukemia.”

Cortes said that studies with venetoclax (Venclexta) in AML (FIGURE 1-3) will also be discussed. “We will present [findings] from the initial phase 1 and phase 2 trials and then the randomized phase 3 studies that cemented venetoclax as the standard of care in a short period of time.”

Results of the phase 3 Viale-A (NCT02993523) trial led to venetoclax being adopted as the standard treatment in older patients with previously untreated AML. The trial randomized 286 patients to receive azacitidine plus venetoclax and 145 patients to receive azacitidine plus placebo. At a median follow-up of 20.5 months, the median OS was 14.7 months in the azacitidine/venetoclax group vs 9.6 months in the control group (HR for death, 0.66; 95% CI, 0.52-0.85; P < .001). Participants were also more likely to experience CR (36.7% vs 17.9%; P < .001) and composite CR (66.4% vs 28.3%; P < .001). Serious adverse events occurred in 83% of patients in the experimental arm vs 73% of patients in the control arm.3 These data, as well as data from the phase 3 VIALE-C trial (NCT03069352), supported the FDA decision in October 2020 to grant regular approval to venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of adults 75 years and older with newly diagnosed AML.4,5

Another major focus of conversation will be research indicating that many patients with CML who have responded completely to TKI treatment and gone several years with no evidence of disease can safely discontinue treatment.

“We have [an] increasing amount of trial data on this issue,” Cortes said. “We want to present the data from The LAST Study [NCT02269267] and elsewhere and put those trials in context and explore which patients are good candidates for treatment discontinuation and how we can do it right to minimize the risk for patients.”

**EXPANDING HORIZONS**

Cortes credits his career in medicine to his uncle. “When I was in high school, I wanted to be a dentist for some reason, but my uncle, Jorge E. Cortes, MD

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**Drug development is a very complex endeavor. Having a drug that works is obviously very important, but you have to design the trials in such a way that you get not only the academic answers and the clinical answers that you want, but also the data you need for regulatory approval.”**

—Jorge E. Cortes, MD

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**HONORS & AWARDS**

**2019**
- Director, Georgia Cancer Center

**2018**
- 2018 International Chronic Myeloid Leukemia Foundation Goldman Prize

**2016**
- Cattlemen for Cancer Research Hero Award

**2011**
- Otis W. and Pearl L. Walters Faculty Achievement Award in Clinical Research, The University of Texas MD Anderson Cancer Center

**2007**
- Service to Mankind Award, The Leukemia & Lymphoma Society

**2005**
- Celgene 2005 Young Investigator Achievement Award for Clinical Research in Hematology

**2003**
- Faculty Scholar Award, The University of Texas MD Anderson Cancer Center

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**LEUKEMIA, CONTINUED ON PAGE 46**
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• The latest developments in CAR T-cell therapy
• The increasing importance of genomics and molecular testing in hematologic malignancies
• How to cope with the emerging value-based care landscape

PROGRAM CO-CHAIRS

Andre H. Goy, MD
John Theurer Cancer Center
Hackensack, NJ

Jorge E. Cortes, MD
Augusta University
Augusta, GA

Sagar Lonial, MD, FACP
Winship Cancer Institute of Emory University
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leukemia

SHAPING THE NEXT GENERATION

You could say that Cortes enjoys being in the weeds of drug development, having a hand in the process from start to finish. He enjoys the complexity of running large drug trials, analyzing early-stage data to construct late-stage protocols, assembling research teams, and working with both drug companies and the FDA.

“Drug development is a very complex endeavor,” he said. “Having a drug that works is obviously very important, but you have to design the trials in such a way that you get not only the academic answers and the clinical answers that you want, but also the data you need for regulatory approval. You also need to work with a lot of different groups—investigators, sponsors, regulatory authorities, and most importantly, you have to work with patients. You need to recruit and enroll them.”

Cortes noted that one of the key challenges is adapting opinions about drugs as new information becomes available and modifying trial design accordingly.

“Even when the drugs look good initially, you also have to acknowledge that you know very little, and sometimes you learn things that you didn’t expect,” he said, citing his experience with the agent ponatinib. “It looked like a wonderful, very effective drug, but we learned that ponatinib had risk of arterial occlusive events—heart attacks, strokes, and things like that—which was completely unexpected. The challenge was how to react to that. How do you balance the risk-benefit ratio? How do you [work] with the sponsor, the regulator agencies, and the patients?”

Cortes’ strategy for managing these adverse effects secured ponatinib its 2012 FDA approval—albeit with a black box warning—for the treatment of adults with CML and Philadelphia chromosome-positive ALL. Last year, the FDA expanded the indication. Both approvals were supported by data from the phase 2 PACE trial (NCT01207440); the second indication was also supported by data from the phase 2 OPTIC trial (NCT02467270).

“When we talk about what it takes to run a good trial, it all sounds straightforward, almost to the point of being obvious, but it’s not,” DiNardo said. “Doing good clinical research is a challenge, and some people are much better at it than others. I worked with Dr Cortes on several trials when I was new to the leukemia team at MD Anderson, and I am very happy I got a chance to learn from the best.”

LOOKING BEYOND THE CURVE

Among the discussion of new trial results and new diagnostic tests, the International Congress on Hematologic Malignancies® will also explore a relatively new concern: weighing the relative value of various potential treatments beyond their statistical significance.

“You’re looking to maximize value for the patient,” Cortes said. “In a randomized trial, you [are looking to] get an improvement in survival that has a statistical value. But statistical significance may or may not mean something clinically. If [the survival benefit]...
is just a few weeks and the toxicity profile is harsh, how much of that extra time is spent in the hospital or suffering because of adverse effects? The survival benefit can be somewhat diluted by what kind of lifestyle you have. You’re alive, but are you living a normal life or at least close-to-normal life? And then, you know, how much are you paying for each week or month of extended survival? These are all things you need to consider, and we’re seeing more interest in thinking about how to balance them.”

Cortes has taken a particular interest in improving quality of life for older patients and those with comorbidity that made traditional treatments hard to tolerate. “Age alone doesn’t make you less able to tolerate treatment, but it is more common that older patients will not be able to tolerate treatment,” he said.

Cortes’ interest in investigating treatments for older patients helped inspire his work to develop glasdegib. The agent was approved in November 2018 in combination with low-dose cytarabine for patients with newly diagnosed AML who are 75 years or older with comorbidities that preclude intensive induction chemotherapy. That approval was supported by data from the BRIGHT AML 1003 trial (NCT01546038), in which 115 patients were randomized to receive low-dose cytarabine with or without glasdegib. After a median follow-up of 20 months, median OS was 8.3 months (95% CI, 4.4-12.2) in the investigative arm vs 4.3 months (95% CI, 1.9-5.7) in the control arm (HR, 0.46; 95% CI, 0.30-0.71; P = .0002).

“[Older patients] have more comorbidities; they frequently take other medications, so you have to consider drug-drug interactions,” Cortes said. “There is also a tendency to give up—patients give up on themselves, doctors are more likely to give up on [finding treatments]—and you need to avoid that. Life expectancy is much longer now than it was 30 years ago. For trial [design] purposes, we used to consider patients over 55 [years] as elderly. We wouldn’t even [enroll them to] stem cell trials. Nowadays that sounds ridiculous. We realize that it’s just as important to combat cancer in these patients as it is in patients of any other age.”

CARVING OUT A CORNER OF CARE

To relax and recharge, Cortes naturally enjoys something that keeps him moving full speed ahead: long-distance running. “I love to run. I have done 8 marathons so far. I’ve run them in Chicago, Boston, New York, and Houston. I’ll be doing Houston again [in 2022], and hopefully that will qualify me to return to Boston,” said Cortes, whose best marathon time is 3 hours and 30 minutes.

Why running? Part of the allure is the chance to get away from stuffy indoor spaces and spend long periods outside. He even enjoys bad-weather days because he likes making himself endure conditions that would send others to the treadmill.

“The challenge is the point of long-distance running. It’s demanding. The race is demanding. The training is demanding. But it gives you a feeling of accomplishment,” he said. “I also like that it’s an individual sport. If I have a bad day, I’m not hurting any teammates. Running lets you run your race, at your own pace. You set your goals, and it’s fun to meet them. But if you don’t, you just try again.”

REFERENCES

8. FDA approves glasdegib for AML in adults age 75 or older or who have comorbidities. FDA. Updated December 14, 2018. Accessed October 26, 2021. bit.ly/3vOy3jb
For appropriate patients faced with relapsed/refractory multiple myeloma

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INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

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

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

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

ADC = antibody-drug conjugate; BCMA = B-cell maturation antigen; RRMM = relapsed or refractory multiple myeloma.

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verification and description of clinical benefit in a confirmatory trial(s).

Continued approval for this indication may be contingent upon

refractory multiple myeloma who have received at least 4 prior therapies,

BLENREP is indicated for the treatment of adults with relapsed or

RRMM = relapsed or refractory multiple myeloma.

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Because of the risk of ocular toxicity, BLENREP is available

based on severity.

Conduct ophthalmic exams at baseline, prior to each dose,

in changes in vision, including severe vision loss and corneal

BLENREP caused changes in the corneal epithelium resulting

in 18% of 218 patients in the pooled safety population, including

Infusion-related reactions occurred in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transpeptidase increased (5%).

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcaemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

**USE IN SPECIFIC POPULATIONS**

**Lactation:** Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

** Females and Males of Reproductive Potential:** Based on findings in animal studies, BLENREP may impair fertility in females and males.

**Geriatric Use:** Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

**Renal or Hepatic Impairment:** The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
BLENREP
(belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

## WARNIMG: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcers, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.2)].

## 1 INDICATIONS AND USAGE

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

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

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 169), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (definite of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

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

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 3 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1) of full Prescribing Information].

Changes in visual acuity may be associated with difficulty in driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].

## 5.2 BLENREP REMS

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)].

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available at www.BLENREPREMS.com and 1-855-209-9188.

## 5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenia event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

## 5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)]. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer predmedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

## 5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

## 6 ADVERSE REACTIONS

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

- Ocular toxicity [see Warnings and Precautions (5.1)].
- Thrombocytopenia [see Warnings and Precautions (5.3)].
- Infusion-related reactions [see Warnings and Precautions (5.4)].

### 6.1 Clinical Trials Experience

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

The pooled safety population described in Warnings and Precautions is reflected exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP.

Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

(continued on next page)
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP: keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (>20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (>5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

### Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Keratopathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>53</td>
</tr>
<tr>
<td>Blurred vision&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22</td>
</tr>
<tr>
<td>Dry eyes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>14</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions&lt;sup&gt;e&lt;/sup&gt;</td>
<td>21</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup)f&lt;/sup&gt;</td>
<td>11</td>
</tr>
</tbody>
</table>

<sup>a</sup> Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.

<sup>b</sup> Visual acuity changes were determined upon eye examination.

<sup>c</sup> Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

<sup>d</sup> Dry eyes included dry eye, ocular discomfort, and eye pruritus.

<sup>e</sup> Fatigue included fatigue and asthenia.

<sup>f</sup> Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

- **Eye Disorders:** Photophobia, eye irritation, infective keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders:** Vomiting.
- **Infections:** Pneumonia.
- **Investigations:** Albuminuria.

---

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

### Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Creatine phosphokinase increased</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

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

**Data**

**Animal Data:** Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

(continued on next page)
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception

Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility

Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats [see Nonclinical Toxicology (13.1) of full Prescribing Information].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Toxicity

• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].

• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Ide-Cel Maintains Clinical Activity With Long-term Follow-up in Relapsed/Refractory Multiple Myeloma

by JESSICA HERGERT

IDECACTAGENE VICLEUCEL (ide-cel; Abecma) continued to elicit frequent, deep, and durable responses among patients with heavily pretreated relapsed/refractory multiple myeloma irrespective of whether patients received 3 or at least 4 prior therapies. These responses were reflected in updated efficacy and safety results from the phase 2 KarMMa trial (NCT03361748) presented during the 18th International Myeloma Workshop. ¹

At a median follow-up of 24.8 months (range, 1.7-33.6), the overall response rate (ORR) was 73% in all patients treated with chimeric antigen receptor (CAR) T-cell therapy (n = 128). Moreover, the complete response (CR) rate was 33%.

The median duration of response (DOR) was 10.9 months (95% CI, 9.0-11.4), the median progression-free survival (PFS) was 8.6 months (95% CI, 5.6-11.6), and the median overall survival (OS) was 24.8 months (95% CI, 19.9-31.2) for patients in the efficacy population treated with ide-cel.

Notably, the ORR, CR rate, and PFS were most prominent when ide-cel was given at the highest target dose (450 x 10⁶ CAR-positive T cells) at 81%, 39%, and 12.2 months, respectively. The median OS was 22 months (95% CI, 10.0-not evaluable [NE]) vs 25.2 months (19.9-NE) for patients who received 3 or 4 or more prior lines of therapy, respectively.

“The favorable benefit-risk profile of ide-cel [observed] regardless of the number of prior lines of therapy supports its role as a treatment option of [patients with] heavily pretreated relapsed/refractory multiple myeloma,” lead study author Larry D. Anderson Jr, MD, PhD, associate professor in the Department of Internal Medicine of the Division of Hematology/Oncology at the Harold C. Simmons Comprehensive Cancer Center of UT Southwestern Medical Center in Dallas, Texas, said in a virtual presentation of the data.

On March 26, 2021, the FDA approved ide-cel as the first cell-based gene therapy in multiple myeloma for the treatment of patients with relapsed/refractory multiple myeloma who had progressed on 4 or more prior lines of therapy, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody.² The regulatory decision was based on prior findings from the KarMMa trial, in which ide-cel induced an ORR of 72% (95% CI, 62%-81%) among 127 treated patients, with a CR rate of 28% (95% CI, 19%-38%). Further, an estimated 65% of patients who achieved CR remained in CR for at least 12 months and investigators reported a favorable safety profile in this patient population.

KARMA STUDY DESIGN

Investigators enrolled patients with relapsed/refractory disease who had received at least 3 prior regimens with at least 2 consecutive cycles each or best response of progressive disease. Patients must have been previously exposed to an IMiD, a PI, and a CD38-directed monoclonal antibody and refractory to their last prior therapy per International Myeloma Working Group criteria.

Patients underwent leukapheresis followed by bridging therapy at least 14 days before lymphodepletion, which consisted of 30 mg/m² of fludarabine plus 300 mg/m² of cyclophosphamide on days -5, -4, -3, and 0. Patients then received a single infusion of ide-cel. ORR served as the primary end point of the study, with CR rate, safety, DOR, PFS, OS, pharmacokinetics, minimal
residual disease, quality of life, and health economics and outcomes research as key secondary end points.

In the overall population, the median age was 61 years (range, 33-78) and 59% of patients were male. More than half of patients had an ECOG performance status of 1 (53%) and stage II disease (70%) per revised International Staging System criteria. Additionally, 35% of patients had high-risk cytogenetics, 51% had high tumor burden, 85% had tumor B-cell maturation antigen expression of at least 50%, and 39% had extramedullary disease.

The median time since initial diagnosis was 6 years (range, 1-18). Patients received a median of 6 (range, 3-16) prior antitumor regimens. Nearly all patients (94%) underwent prior autologous stem cell transplant (ASCT); 34% underwent more than 1 ASCT, and 88% of patients received any bridging therapies for multiple myeloma. Nearly all (94%) of patients were refractory to a CD38-directed monoclonal antibody, 84% were triple-class refractory, and 26% were penta-class refractory.

**STRATIFIED RESULTS OF THE KARMMA TRIAL**

By number of prior treatments, the ORR was 73% in patients with 3 prior lines of therapy (n = 15) and 73% in patients with at least 4 prior lines of therapy (n = 113). The CR rates were 53% and 30%, respectively. In both groups, 20% of patients obtained a partial response (PR); 23% of patients with at least 4 prior therapies achieved a very good partial response (VGPR).

The median DOR was 8.0 months (95% CI, 3.3-11.4) in patients with 3 prior lines of therapy and 10.9 months (95% CI, 9.2-13.5) in patients with at least 4 prior lines of therapy. The 24-month event-free DOR rates were 18.2% vs 21.3%, respectively. When measuring DOR by response, the median DOR was 21.5 months (95% CI, 12.5-NE), 10.4 months (95% CI, 5.1-12.2), and 4.5 months (95% CI, 2.9-6.7) in those who achieved greater than CR, VGPR, and PR, respectively.

The median PFS was 8.6 months (95% CI, 2.9-12.1) vs 8.9 months (95% CI, 5.4-11.6), for those who received 3 and 4 or more lines of prior treatment, respectively. Overall, the 1-year, 1.5-year, and 2-year OS rates were 78%, 65%, and 51%, respectively. The median OS exceeded 20 months across several key high-risk patient subgroups, Anderson explained (TABLE 1).

The median OS was 21.7 months (95% CI, 17.1-31.2) months in patients under 65 years vs 28.3 months (95% CI, 20.2-NE) in those at least 65 years. In patients without high-risk cytogenetics, the median OS was 31 months (95% CI, 20.2-NE) vs 19.9 months (95% CI, 12.8-NE) in those with high-risk cytogenetics.

Additionally, the median OS was NE (95% CI, 21.3-NE) in patients without extramedullary disease vs 20.2 months (95% CI, 15.5-28.3) in those with extramedullary disease. For patients without triple-refractory disease, the median OS was 31.2 months (95% CI, 19.9-NE) compared with 21.7 months (95% CI, 18.2-NE) in those with triple-class refractory disease.

Regarding safety in the overall population, 84% of patients reported at least 1 cytokine release syndrome (CRS) event; 78% of these were grade 1 or 2, 4% were grade 3, and less than 1% were grade 4 or grade 5. The median time to onset of CRS was 1 day (range, 1-12) and the median duration of CRS was 5 days (range, 1-63).

At least 1 neurotoxicity event occurred in 18% of patients treated with ide-cel; 9% of these were grade 1, 5% were grade 2, and 4% were grade 3. The median time to onset of neurotoxicity was 2 days (range, 1-10) and the median duration of neurotoxicity was 3 days (range, 1-26). The incidences of CRS and neurotoxicity were similar in patients who received 3 or at least 4 prior lines of therapy and consisted of mostly low-grade events.

Regarding adverse effects (AEs) of special interest, similar rates of infections and secondary primary malignancies were observed with the longer follow-up. Additionally, no unexpected gene therapy-related toxicities were reported with ide-cel.

Any-grade hematologic AEs of interest in the overall population included neutropenia (91%), anemia (70%), thrombocytopenia (64%), leukopenia (42%), and lymphopenia (28%). Of these, 89%, 61%, 52%, 39%, and 27% of events were grade 3 or 4, respectively. All-grade nonhematologic AEs of interest included infections (70%), secondary primary malignancies (7%) and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (3%). Of these, 27%, 2%, and 2% were grade 3 or 4, respectively.

The median time to recovery of grade 3 or higher neutropenia and thrombocytopenia was 2 months. Ide-cel is being further evaluated in ongoing phase 1, 2, and 3 clinical trials of multiple myeloma, including the phase 2 KarMMa-2 (NCT03601078), the phase 3 KarMMa-3 (NCT03651128), the phase 1 KarMMa-4 (NCT04196491), and the phase 1/2 KarMMa-7 (NCT04855136) trials.

For a full list of references, see the article at bit.ly/3D3pTGI.

**TABLE. Overall Survival in High-Risk Patient Subgroups in the KarMMa Trial**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years (n = 83)</td>
<td>21.7 (17.1-31.2)</td>
</tr>
<tr>
<td>Age ≥ 65 years (n = 83)</td>
<td>28.3 (20.2-NE)</td>
</tr>
<tr>
<td>High-risk cytogenetics</td>
<td></td>
</tr>
<tr>
<td>No (n = 66)</td>
<td>31.0 (20.2-NE)</td>
</tr>
<tr>
<td>Yes (n = 45)</td>
<td>19.9 (12.8-NE)</td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td></td>
</tr>
<tr>
<td>No (n = 78)</td>
<td>NE (21.3-NE)</td>
</tr>
<tr>
<td>Yes (n = 50)</td>
<td>20.2 (15.5-28.3)</td>
</tr>
<tr>
<td>Triple-refractory disease</td>
<td></td>
</tr>
<tr>
<td>No (n = 20)</td>
<td>31.2 (19.9-NE)</td>
</tr>
<tr>
<td>Yes (n = 108)</td>
<td>21.7 (18.2-NE)</td>
</tr>
</tbody>
</table>

NE, not estimable; OS, overall survival.
IN HER2+ EARLY BREAST CANCER (EBC), UNDERSTAND HER RISK OF RECURRENCE

HER2 = human epidermal growth factor receptor 2.
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.¹

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.¹
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.  

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.

**Association between pCR and event-free survival (EFS)** in the HER2+ subgroup analysis of the CTNeoBC study\(^1\)

*EFS was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.\(^1\)

1,989 patients with HER2+ tumors were included in the subgroup analysis. 55% of which did not receive a full year of adjuvant HER2-targeted monotherapy treatment.\(^1\)

**While there are different paths you can choose for your patient with HER2+ EBC, her treatment shouldn’t stop at neoadjuvant therapy.**
Discover possible adjuvant treatment options that may be right for her*:

For patients who achieve pCR, visit PCRinEBC.com

For patients who do not achieve pCR, visit NoPCRinEBC.com

*There may be other treatment options available for your patients.

Daratumumab Combination Therapy Emerges as New Standard

by DARLENE DOBKOWSKI, MA

**UPDATED EFFICACY DATA FROM** the phase 3 MAIA study (NCT02252172) showed that daratumumab (Darzalex) plus lenalidomide (Revlimid) and dexamethasone (DRd) provided a significant overall survival (OS) and progression-free survival (PFS) benefit compared with lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Philippe Moreau, MD, professor of clinical hematology and head of the Hematology Department at Nantes University Hospital in France, presented the data during the 18th International Myeloma Workshop.

At a median follow-up of 56.2 months, the median OS was not reached in either group (HR, 0.68; 95% CI, 0.53-0.86; \( P = .0013 \)). The estimated OS rate at 5 years was 66.3% in the DRd arm (n = 368) vs 53.1% in the Rd (n = 369) group.

The updated median PFS was not reached in the DRd arm vs 34.4 months in the Rd arm (HR, 0.53; 95% CI, 0.43-0.66; \( P < .0001 \)). The 60-month PFS rates were 52.5% vs 28.7%, respectively. "Those results, when looking at [DRd], both for PFS and OS and a relatively good safety profile, I would say, are now establishing [that combination] as a new standard of care for patients that are not transplant eligible," Moreau said.

The MAIA investigators analyzed data from 737 patients with newly diagnosed multiple myeloma. These patients were ineligible for high-dose chemotherapy and autologous stem cell transplantation because of their age (older than 65 years) or the presence of comorbidities. Participants’ median age was 73 years (range, 45-90).

“One very important point and theory... for elderly patients we know that many of them are not able to receive 2 or 3 lines of treatment, so this suggests that the most effective treatment should be used up front and not saved for relapse," Moreau said. The primary end point was PFS, with key secondary end points including OS, time to second PFS event, overall response rate (ORR), complete response (CR) and stringent CR (sCR) rate, and minimal residual disease as determined by next-generation sequencing with 10^4 sensitivity.

At 56.2 months follow-up 42% of patients remained on treatment with DRd compared with 18% on Rd. Of those who discontinued treatment, the most common reasons included progressive disease (27% vs 34%, respectively), adverse events (13% vs 23%), and nonadherence with study drug (5% vs 8%). Patient death accounted for 7% of discontinuations in both arms.

In terms of response to treatment, DRd induced deeper responses with higher rates of CR, sCR, and very good partial response (VGPR) compared with primary efficacy data (TABLE 1). With 28 more months of follow-up, the ORR for patients in the DRd arm was 93%, which included a 35% sCR rate, a 16% CR rate, a 30% VGPR rate, and a 12% partial response (PR) rate. For those in the Rd arm, the ORR was 82% with a CR rate of 15%, an sCR rate of 15%, a VGPR rate of 27%, and a PR rate of 25%.

In a post hoc analysis, investigators reported that treatment with DRd resulted in a robust PFS benefit among patients who received treatment for 18 months or longer. Specifically, the median PFS for the 289 patients who received DRd at this threshold was not reached compared with 54.8 months among the 204 patients in the Rd arm (HR, 0.57; 95% CI, 0.43-0.76; \( P < .0001 \)). The 60-month PFS rates for this subgroup were 64.4% vs 44.6%, respectively.

The median time to next treatment was not reached with DRd vs 42.4 months with Rd (HR, 0.47; 95% CI, 0.37-0.59; \( P < .0001 \)). In the DRd arm, 114 patients went on to subsequent therapy, the most common of which was proteasome inhibitor containing regimen without an immunomodulatory agent (53%). This was the therapy of choice for 54% of the 186 patients in the Rd arm who received subsequent therapy. Further daratumumab-containing regimens were received by 15% and 46% of patients at any line of subsequent therapy, respectively.

Longer follow-up did not result in new safety concerns (TABLE 2).

**TABLE 1. Updated ORR Data in MAIA Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary analysis (median follow-up 28 months)</th>
<th>Updated analysis (median follow-up 56.2 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Rd (n = 364)</td>
<td>Rd (n = 365)</td>
<td>D-Rd (n = 366)</td>
</tr>
<tr>
<td>ORR</td>
<td>93%</td>
<td>82%</td>
</tr>
<tr>
<td>sCR</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>CR</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>VGPR</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>PR</td>
<td>14%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**TABLE 2. Most Common Grade 3/4 TEAEs in MAIA Trial**

<table>
<thead>
<tr>
<th>Nonhematologic, n (%)</th>
<th>D-Rd (n = 364)</th>
<th>Rd (n = 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>79 (21%)</td>
<td>39 (11%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>46 (13%)</td>
<td>36 (10%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>40 (11%)</td>
<td>39 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (9%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (9%)</td>
<td>16 (4%)</td>
</tr>
</tbody>
</table>

**REFERENCE**

Moreau P, Facon T, Kumar SK, et al. Overall survival and progression-free survival by treatment duration with daratumumab + lenalidomide/dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: phase 3 MAIA study. Presented at: 18th International Myeloma Workshop; September 8-11, 2021; Vienna, Austria.
## Data Confirm Efficacy of Fixed-Volume Isatuximab-Based Regimen for Newly Diagnosed Disease

by BRITTANY LOVELY

### THE SAFETY AND EFFICACY of the quadruplet regimen of fixed-dose isatuximab-irfc (Sarclisa) in combination with bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (Isa-VRd) were confirmed for patients with newly diagnosed multiple myeloma with no immediate intent for autologous stem cell transplant, based on updated results from a phase 1b trial (NCT02513186) presented at the 18th International Myeloma Workshop.1

Part B of the study assessed the efficacy of Isa-VRd in 46 patients who were ineligible or had no immediate intent for autologous stem cell transplant. At a median follow-up of 15.24 months, the overall response rate was 97.8%, including a 53.3% complete response rate, 37.8% very good partial response rate, and 6.7% partial response rate.

Minimal residual disease (MRD) negativity was calculated using combined next-generation flow cytometry or sequencing methods at a threshold of 105. Of the 45 patients who had a response, 23 (51.1%) had MRD negativity.

“The good efficacy of the approved short-duration, fixed-volume infusion of isatuximab in combination with VRd [confirms the feasibility of this regimen for] patients with newly diagnosed multiple myeloma who are ineligible for transplant or who have no immediate intent for transplant,” said Enrique M. Ocío, MD, PhD, head of the Hematology Department at Marqués de Valdecilla University Hospital in Santander, Cantabria, Spain, in a presentation of the data.

The quadruplet therapy is the standard of care for patients who are ineligible for autologous stem cell transplant. In part B of the trial, investigators evaluated isatuximab as a fixed-dose infusion; in part A, isatuximab was assessed as a weight-based infusion. In part B, isatuximab was administered at 10 mg/kg from a 250 mL fixed-volume infusion—the standard dilution volume of the approved indications for the CD38 monoclonal antibody—for 4 six-week cycles with standard-dose VRd. This was followed by maintenance therapy with isatuximab, lenalidomide, and dexamethasone for 28 days or until disease progression, unacceptable toxicity, or willingness to discontinue.

The median duration of treatment for patients in part B was 15.3 months (range, 1.4-21.4) with patients receiving a median of 14 treatment cycles (range, 1-21).

A marked improvement was observed within the median duration of infusion, proving the fixed-dose infusion to be a more convenient treatment option for patients. Specifically, in part B, the median duration of the fixed-volume isatuximab infusion decreased from 3 hours and 41 minutes for the first infusion to 1 hour and 55 minutes for the second infusion and 1 hour and 20 minutes for the third. The median durations of infusion in part A were 3 hours and 44 minutes, 2 hours and 49 minutes, and 2 hours and 17 minutes, respectively.

Patients enrolled in part B of the study had a median age of 70 years (range, 49-87), with a majority (65.2%) of patients aged at least 65 to 74 years. Of the treated patients, 13 (28.3%) were eligible but had no intent for autologous stem cell transplant. Of these patients, 7 proceeded to stem cell mobilization, and data for 6 were reported: 2 received granulocyte colony-stimulating factor, 2 received plerixafor (Mozobil), and 2 received a combination of these treatments.

At data cutoff of March 17, 2021, 30 patients (65.2%) remained on study treatment. Of the 16 who discontinued treatment, reasons including poor adherence to protocol or withdrawal by subject were reported for 1 patient each, progressive disease or procession to autologous stem cell transplant were reported for 3 patients each, and treatment-emergent adverse effects (TEAEs) were reported as a reason for 8 patients.

Specifically, regarding TEAEs, diverticulitis, metastatic malignant melanoma, peripheral sensory neuropathy, cerebral venous sinus thrombosis, acute respiratory distress syndrome, and hepatocellular carcinoma were reported in 1 patient each. COVID-19 was reported as the reason for discontinuation in 2 patients. No new safety signals were reported with Isa-VRd, Ocío said.

Investigators noted that the fixed-volume infusion administered in part B reduced the incidence and severity of infusion-related reactions compared with the weight-based infusion in part A. Specifically, infusion reactions (IRs) occurred in 63% of patients (n = 27) in part A vs 28% of patients (n = 13) in part B. Most IRs were grade 2. Of note, 1 grade 3 IR was reported in part A and led to discontinuation; no grade 3 IRs were reported for part B.

Most IRs occurred during the first infusion in both study groups (76.5% in part A and 76.9% in part B). All other IRs occurred at infusion 3 or later.

The quadruplet therapy is under investigation in 2 ongoing phase 3 trials. The first, IMROZ (NCT03319667), is assessing the combination in patients with newly diagnosed multiple myeloma who are ineligible for transplant. The second, GMMG HD7 (NCT03617731), is evaluating the efficacy of the addition of isatuximab to VRd and lenalidomide maintenance vs VRd and lenalidomide maintenance alone.

### REFERENCES


NOW ENROLLING: Clinical Trials for Lung Cancer with TIL Cell Therapy

Investigational

Ph 2 Clinical Trials
Multi-Center
Non-Randomized
Non-Placebo Controlled

LN-145 (TUMOR INFILTRATING LYMPHOCYTES; TIL) is an investigational, personalized immunotherapy derived from the patient’s own immune cells.

KEY ELIGIBILITY CRITERIA:

- Diagnosis of Metastatic Non-small Cell Lung Cancer
- Disease progression after 1 or more lines of prior therapy which may have been a checkpoint inhibitor
- PD-L1 positive or negative status
- Tumors with EGFR, ALK, ROS mutations acceptable
- ECOG PS 0 - 1 (Fully active or able to carry out light work or activity)
- At least one tumor that can be safely removed by surgery for TIL and a second measurable tumor for response assessment

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.

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and effectiveness of this study has not been determined.

FOR MORE INFORMATION

CALL CENTER 1-866-565-4410, select option 3
EMAIL clinical.inquiries@iovance.com

CLINICALTRIALS.GOV
Lung Trial: NCT04614103
Solid tumor trial NSCLC cohorts: NCT03645928
Enobosarm Study Aims to Establish New Class of Endocrine Treatment in MBC

by KYLE DOHERTY

THE VIRILIZING EFFECTS OF androgen agents previously limited their use in the treatment of breast cancer. Investigators hope to improve upon the efficacy and tolerability of androgens with the October 13, 2021, initiation of the phase 3 ARTEST trial (NCT04869943).1,2

Investigators will examine the efficacy of enobosarm in patients with androgen receptor (AR)-positive, estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer (MBC) who have experienced tumor progression after treatment with estrogen-blocking agents and CDK 4/6 inhibitors.

In normal breast tissue, androgens inhibit cellular proliferation. AR is the most abundantly expressed sex hormone receptor in breast cancers; 70% to 95% of breast cancers are AR-positive and AR is recognized as a prognostic marker for outcomes to breast cancer treatment. In ER-positive breast cancer, AR agonists previously have been shown to inhibit tumor growth, and an unmet need exists for those patients who have exhausted ER-targeting agents.2

“Enobosarm is a nonsteroidal selective AR agonist,” said Erica L. Mayer, MD, MPH, a senior physician and breast cancer medical oncologist at Dana-Farber Cancer Institute in Boston, Massachusetts. “It binds to the AR and helps to suppress the growth of hormone receptor–positive breast cancer cells in vitro. This [process] works particularly well in models where the disease is resistant to prior endocrine therapies.” Mayer added that this observation led to the interest in studying the mechanism in patients who have undergone prior endocrine therapy.

INITIAL EFFICACY AND SAFETY DATA OF ENOBOSARM

ARTEST investigators will build on previously reported efficacy and safety data from a phase 2 trial (NCT02463032) of enobosarm. In the phase 2 trial, participants had AR-positive, ER-positive, HER2-negative MBC; were heavily pretreated; and had progressed after treatment with multiple lines of endocrine therapy. The open-label, multinational trial enrolled 136 postmenopausal women to be treated with either enobosarm 9 mg (n = 72) or enobosarm 18 mg (n = 64). The study’s primary efficacy end point was to determine clinical benefit rate (CBR) by RECIST 1.1 in patients with AR-positive disease treated at 6 months.2,3

AR status was centrally assessed, centrally and patients with 10% or greater AR-positivity were included in the study. Patients with AR-negative, not determined, or uninformative status were not evaluable. Patients needed to have responded to adjuvant endocrine therapy for at least 3 years or to their most recent endocrine therapy for metastatic disease for at least 6 months to be included in the trial.

The median age in the 9-mg cohort was 60.5 years (range, 35-83) and 62.5 years (range, 42-81) in the 18-mg cohort. Prior chemotherapy was administered in 90% and 92.3% of patients in the 9-mg group and the 18-mg group, respectively. The median number of prior lines of endocrine therapy was 3 for both dose levels.

Among the 50 efficacy-evaluable patients in the 9-mg cohort, the CBR at 24 weeks was 32% (95% CI, 19.5%-46.7%). The 24-week CBR in the 18-mg group (n = 52) was 29% (95% CI, 17.1%-43.1%).1

Investigators noted a correlation between radiographic progression-free survival (rPFS) and the degree of AR nuclei staining. In an exploratory analysis, investigators determined that 40% AR staining was the optimal cutoff point for differentiating the benefit of treatment with enobosarm. The median rPFS for patients with greater than 40% AR staining (n = 24) was 5.5 months versus 4 months (95% CI, 2.1%-17.7%) for patients with 0% to 39% AR staining (n = 26).

Eligibility criteria

- 18 years or older
- ECOG performance status of ≤ 2
- Measurable disease per RECIST 1.1
- AR nuclei staining ≥ 40% as assessed by central laboratory
- Received at least 2 prior lines of treatment in MBC setting which must have included both an AI (monotherapy or combination) and fulvestrant (monotherapy or combination); at least 1 must have been given in combination with a CDK 4/6 inhibitor
- Previously responded without disease progression at least 6 months to 1 of the following treatments: fulvestrant monotherapy, fulvestrant plus CDK 4/6 inhibitor, nonsteroidal AI monotherapy or nonsteroidal AI plus CDK 4/6 inhibitor for MBC
- AR-positivity were included in the study
- Measurable disease per RECIST 1.1
- ECOG performance status of ≤ 2
- 18 years or older

End points

Primary
- rPFS

Select secondary
- ORR

FIGURE. Enobosarm for the Treatment of Metastatic AR-positive, ER-positive, HER2-negative MBC

<table>
<thead>
<tr>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral enobosarm 9 mg/day</td>
</tr>
<tr>
<td>Exemestane monotherapy, exemestane plus everolimus, or selective ER modulator</td>
</tr>
</tbody>
</table>

CI, confidence interval; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; rPFS, radiographic progression-free survival; AI, aromatase inhibitor; AR, androgen receptor; ER, estrogen receptor; MBC, metastatic breast cancer; ORR, objective response rate; rPFS, radiographic progression-free survival.
compared with 2.75 months for patients with less than 40% AR staining (n = 22). The objective response rate (ORR) was 50% vs 0%, respectively, and the CBR was 79% vs 18%, respectively (P < .0001).1

In terms of safety, most adverse effects (AEs) reported in the study were grade 1/2. Serious AEs occurred at a rate of 10.7% vs 16.4% in the 9-mg group and 18-mg group, respectively. No treatment-emergent AEs that led to death were observed.

Investigators concluded that AR could potentially be utilized as a biomarker to identify a subset of patients with ER-positive and HER2-negative advanced breast cancer who are most likely to respond to enobosarm. They also noted that enobosarm appeared to be safe and well tolerated with no virilizing AEs. The phase 3 dose for the ARTEST trial was determined to be 9 mg, and the threshold for AR-positivity was set at a minimum of 40% AR nuclei staining.

“The 9-mg dose had much less toxicity and performed equally well,” Mayer noted. “This agent has some favorable effects. We always talk about AEs being bad, but this drug actually has some favorable effects, including building muscle mass and treating osteoporosis.”

DETAILS OF THE ARTEST TRIAL
The ARTEST trial is an open-label randomized, active control pivotal study that will enroll approximately 210 adult patients across 49 sites in the United States and Europe (FIGURE1).

Patients will be randomized 1:1 to either the enobosarm treatment group or the control treatment group. Patients in the enobosarm group will be treated with 9 mg of oral enobosarm daily until disease progression or unacceptable AEs are observed. The control group will receive an ER-targeted therapy of the investigator’s choice, limited to exemestane monotherapy, exemestane plus everolimus (Afinitor), or a selective ER modulator.

To be included in the trial, patients must have measurable disease by RECIST 1.1 and an ECOG performance status of 2 or less. Patients must have previously responded to fulvestrant monotherapy, fulvestrant plus CDK 4/6 inhibitor, nonsteroidal aromatase inhibitor monotherapy, or nonsteroidal aromatase inhibitor plus CDK 4/6 inhibitor for MBC.

Patients who have undergone more than 1 course of systemic chemotherapy for the treatment of MBC will be excluded from the study. Patients with a biliary catheter, creatinine clearance less than 30 mL/min as measured by the Cockcroft-Gault formula, or a known hypersensitivity or allergy to enobosarm also will not be eligible.

The primary end point of the trial is efficacy, measured by median rPFS. The secondary end point is ORR. Safety follow-up visits will take place approximately 30 days after the last dose of study drug. After the safety follow-up visit, survival follow-up visits will be done monthly for 1 year and every 90 days after 1 year. The study is expected to be completed by April 30, 2023.

“We try to keep our patients with metastatic hormone receptor–positive breast cancer on endocrine therapies as long as possible, as long as they are effective and controlling the cancer,” Mayer said.

“Eventually, these cancers become resistant to endocrine therapies, and we have to make a jump into the chemotherapy category. That’s a moment we try to put off as long as possible [because] endocrine therapies can be so effective and well tolerated, particularly vs chemotherapy. The hope is that this trial will help to develop a new novel endocrine therapy for our patients that will help effectively treat their cancers and delay the time to transition to chemotherapy.”

REFERENCES

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Oncologist Biotech News
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

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

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Effusion and Edema**

Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%.

**INDICATION AND USAGE**

ZYNLONTA is a trademark of ADC Therapeutics SA.
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (Continued)

Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

**Myelosuppression**
Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%.

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

**Infections**
Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

**Cutaneous Reactions**
Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

**Embryo-Fetal Toxicity**
Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

**ADVERSE REACTIONS**
In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

In LOTIS-2, serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to ADC Therapeutics at 1-855-690-0340.

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

www.zynlontahcp.com
ZYNLONTA™ (loncastuximab tesirine-lyl) for injection, for intravenous use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

INDICATIONS AND USAGE

ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Effusion and Edema. Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

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Embryo-Fetal Toxicity. Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose (see Use In Specific Populations (8.1, 8.2)).

ADVERSE REACTIONS

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

Effusion and Edema

Myelosuppression

Infections

Cutaneous Reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADC-002-201 (LOTIS-2) and ADC-042-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles. In this pooled safety population of 215 patients, the most common (≥20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypalbuminemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies [see Clinical Studies (14.1)]. The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection. Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased. Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2

<table>
<thead>
<tr>
<th>Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigueb</td>
<td>38</td>
<td>1*</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
<td>3*</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>30</td>
<td>2*</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
<td>2*</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
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<tr>
<td>Diarrhea</td>
<td>17</td>
<td>2*</td>
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<tr>
<td>Abdominal paina</td>
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<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>0</td>
</tr>
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<td>Constipation</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
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<tr>
<td>Musculoskeletal painb</td>
<td>23</td>
<td>1*</td>
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<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
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</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>0</td>
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<td><strong>Respiratory Disorders</strong></td>
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</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1*</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
<td>2*</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionb</td>
<td>10</td>
<td>&lt;1*</td>
</tr>
</tbody>
</table>
adverse reactions, including laboratory abnormalities, were thrombocytopenia, anemia, neutropenia, and edema. In this pooled safety population of 215 patients, the most common (>20%) adverse reactions included thrombocytopenia (7%), anemia (12%), neutropenia (32%), and edema (30%). Grade 4 neutropenia occurred in 21% and febrile neutropenia in 3%. Other adverse reactions reported in over 10% of patients included pneumonia, pyrexia, dyspnea, nausea, vomiting, and musculoskeletal pain.

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine-lpyl after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse 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

Animal Data

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-lpyl. The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

Lactation

Risk Summary

There is no data on the presence of loncastuximab tesirine-lpyl or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

Females and Males of Reproductive Potential

ZYNLONTA can cause fetal harm when administered to pregnant women. Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating ZYNLONTA. Contraception

Females Advise women of reproductive potential to use effective contraception during treatment and for 9 months after the last dose.

Infertility

Males Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 6 months after the last dose.

Pediatric Use

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

Geriatric Use

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] ≤ ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).

Selected Other Adverse Reactions

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine-lpyl after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.
Treatment Sequencing Could Change With Complementary Combinations and CAR T Options in B-ALL

by JESSICA HERGERT

SIGNIFICANT PROGRESS WITH RAPIDLY evolving therapies, including blinatumomab (Blincyto), inotuzumab ozogamicin (Besponsa), and chimeric antigen ozogamicin (CAR) T-cell therapy, has been made to extend the median overall survival (OS) and improve outcomes for patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL). Antibody-based therapies and CAR T-cell therapies are not mutually exclusive, according to Elias Jabbour, MD, who added that competitive options have the potential to be complementary if sequenced earlier.

“Until recently, when somebody with ALL relapsed, the outcomes were bad and we didn’t have anything [available to treat them],” said Jabbour, a professor of medicine in the Department of Leukemia of the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston, in an interview with OncLive®. In the interview, Jabbour reviewed his presentation on the practice-changing updates in relapsed/refractory B-ALL presented at the 39th Annual Chemotherapy Foundation Symposium®, a program hosted by Physicians’ Education Resource® (PER®), LLC.

“Over the past few years, we’ve [had] several options [become] available to our patients, [including] the bispecific engagers, antibody-drug conjugates [ADCs], and CAR T-cell therapies, first for pediatric and [adolescent and] young adult [AYA] patients and now for adult patients. Each [therapy] has shown a benefit when compared with standard of care. The question is: How do we optimize the [options] to improve outcomes in ALL?” Jabbour asked.

Although not yet backed by level 1 evidence, a potentially promising therapeutic sequencing strategy could incorporate blinatumomab in combination with inotuzumab ozogamicin as frontline therapy followed by consolidative CAR T-cell therapy, Jabbour explained. He added that this strategy could begin to phase out the use of allogeneic stem cell transplant and chemotherapy in B-ALL because these approaches may not be optimal following CAR T-cell therapy. “Each [option] alone is not great enough. The value of treatment can be further improved,” Jabbour said. “This way we can offer these treatments, which are expensive and not [widely] available, in the most optimal way. We can improve the cure rate instead of giving every agent alone with minimal or acceptable benefit.”

TABLE. Efficacy Results in ZUMA-3 Trial13

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Brexucabtagene autoleucel (n = 54)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCR rate (95% CI)</td>
<td>64.8% (51%-77%)</td>
</tr>
<tr>
<td>CR rate (95% CI)</td>
<td>51.9% (37.8%-65.7%)</td>
</tr>
<tr>
<td>Median duration of remission, months (95% CI)</td>
<td>13.6 (9.4-NE)</td>
</tr>
<tr>
<td>Median DOR, if best response is CR, months (95% CI)</td>
<td>NR (9.4-NE)</td>
</tr>
<tr>
<td>Median DOR, if best response is CRi, months (95% CI)</td>
<td>8.7 (1.0-NE)</td>
</tr>
</tbody>
</table>

CR, complete remission; CRi, complete remission with incomplete blood count recovery; DOR, duration of remission; NE, not estimable; NR, not reached; OCR, overall complete remission.

*Efficacy evaluable population

BLINATUMOMAB AND INOTUZUMAB OZOGAMICIN MAKE A SPLASH IN RELAPSED/REFRACTORY B-ALL

In 2017, the FDA granted a full approval to the monoclonal antibody blinatumomab for the treatment of adult and pediatric patients with relapsed/refractory B-cell precursor ALL.1 The approval was based on findings from the phase 3 TOWER trial (NCT02013167), in which blinatumomab elicited a 44% complete remission (CR) with full, partial, or incomplete hematologic recovery (CRi) rate vs 25% with standard-of-care chemotherapy (P < .001).2 The median OS was 7.7 vs 4 months, respectively (HR, 0.71; 95% CI, 0.55-0.93; P = .01).

Another phase 3 study (NCT02101853) evaluated blinatumomab vs chemotherapy in children and AYA patients with B-ALL in first relapse.3 The 2-year disease-free survival rate was 54.4% with blinatumomab vs 39% with chemotherapy (HR, 0.70; 95% CI, 0.47-0.98; P = .03). The 2-year OS rates were 71.3% vs 58.4%, respectively (HR, 0.62; 95% CI, 0.39-0.98; P = .02).

Also in 2017, the ADC inotuzumab ozogamicin was approved by the FDA for the treatment of adults with relapsed/refractory B-cell precursor ALL based on findings from the phase 3 INO-VATE trial (NCT01564784).4 Updated results showed a 73.8% CR/CRi rate with inotuzumab ozogamicin vs 30.9% with standard-of-care chemotherapy in this patient population (P < .0001).5
COMBINATION REGIMENS SPELL OUT ADDITIONAL SUCCESS
In an ongoing phase 2 study (NCT01371630), inotuzumab ozogamicin in combination with low-intensity mini-hyper-CVD (mini-HVCD), a chemotherapy regimen consisting of cyclophosphamide and dexamethasone at 50% dose reduction, no anthracycline, methotrexate at 75% dose reduction, and cytarabine at 0.5 g/m² for 4 doses, demonstrated encouraging activity in patients with relapsed/refractory Philadelphia chromosome-negative ALL.⁶

Long-term follow-up data from the study showed an overall response rate of 80% with inotuzumab ozogamicin plus mini-HVCD, with a complete response rate of 57% among 96 patients treated. The MRD negativity rate among responders was 83%.

To further expand this regimen, another study evaluated sequential inotuzumab ozogamicin with mini-HVCD with or without blinatumomab as salvage therapy for patients with ALL in first relapse.⁷ The results showed a median OS of 16.5 months with the combination as first-line salvage therapy and 5.8 months as second-line or later salvage therapy, indicating that salvage status affects OS, Jabbour said.

CAR T-CELL THERAPY ENTERS THE RELAPSED/REFRACTORY ARENA
In 2017, the CAR T-cell therapy tisagenlecleucel (Kymriah) became the first gene therapy to be approved in the United States. The regulatory decision made the therapy available for use in pediatric and AYA patients with relapsed/refractory B-ALL.

Updated findings from the phase 2 ELIANA trial (NCT02435849) demonstrated a 24-month OS rate of 66% with tisagenlecleucel in this patient population.⁸ On October 1, 2021, another CAR T-cell product, brexucabtagene autoleucel (brexu-cell; Tecartus) was approved by the FDA for use in adult patients with relapsed/refractory B-ALL.⁹ The decision was based on findings from the phase 1/2 ZUMA-3 trial (NCT02614066), in which a single infusion of brexu-cell elicited a high response rate consisting of durable responses in patients with heavily pretreated relapsed/refractory B-ALL.¹⁰ ¹¹

Of 54 patients in the efficacy population, 64.8% (95% CI, 51%-77%) of patients who received brexu-cell had a CR/CRi (TABLE¹²). Over half of patients (51.9%) obtained a CR. Moreover, the median duration of remission (DOR) was 13.6 months (95% CI, 9.4-not estimable [NE]). The median DOR for those who achieved CR was not reached (95% CI, 9.6-NE) and the median DOR for those who achieved CRi was 8.7 months (95% CI, 1.0-NE).¹³

In previously reported data, nearly all responders (97%) had MRD negativity after treatment with brexu-cell. Regarding safety, grade 3 or higher cytokine release syndrome occurred in 24% of patients who received brexu-cell. Grade 3 or higher neurologic toxicities occurred in 25% of patients.¹⁴

“We just started the journey with CAR T-cell therapy. There is no question that our management of toxicity will improve. We will gain more expertise, so what we see today may not be the case in 5 to 6 years,” Jabbour said.

Jabbour also highlighted that accessibility remains another challenge of CAR T-cell therapy that needs to be overcome. “The accessibility of CAR T-cell therapy is a problem today, but ALL is also a rare disease. We can only become experts if we have patients,” Jabbour added.

“I’d like to know where CAR T-cell therapy benefits patients most. Activity has been shown across refractory populations, but we know that outcomes can be better in patients with minimal to no disease. That is where I see a role for CAR T-cell therapy. I try to cytoreduce and give CAR T-cell therapy after to offer the best outcomes,” Jabbour said.

Capitalizing upon the success demonstrated with CAR T-cell therapy, research efforts are under way to evaluate improved CAR T-cell therapy designs, dual targeting CAR T-cell therapies, allogeneic products, and fractionated CAR T-cell therapies, Jabbour explained. Notably, CAR T-cell therapy could largely replace the need for allogeneic stem cell transplant for patients with B-ALL who have MRD in first remission.

“We are in the best [era because] we have the tools to cure ALL. Everything is ready in our hands. The future involves using less chemotherapy but more targeted approaches.”

—ELIAS JABBOUR, MD

REASONS FOR RECENT SUCCESS IN ADULTS WITH ALL
▶ Addition of TKIs ponatinib ± blinatumomab to chemotherapy in Philadelphia chromosome—positive ALL
▶ Addition of rituximab to chemotherapy in Burkitt and pre-B-ALL
▶ Potential benefit of adding the CD19 antibody construct blinatumomab and the CD22 monoclonal antibody inotuzumab to chemotherapy in salvage and frontline ALL
▶ Advances and approvals of CAR T-cell therapies
▶ Importance of MRD in complete remission at instance of complete remission vs 3 months

ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL; CAR, chimeric antigen receptor; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor.
INDICATION
EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLONGATION and TORSADES DE POINTEES
See full prescribing information for complete boxed warning.

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%),...
Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of 1.2% of patients had a QTc interval >500 msec and 11% of patients

**WARNINGS AND PRECAUTIONS**

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

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

**Diarrhea**

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

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

**Embryo-Fetal Toxicity**

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY.

**ADVERSE REACTIONS**

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

**DRUG INTERACTIONS**

**CYP3A Inducers**

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

**CYP3A Substrates**

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

**Prolonged QTc Interval**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

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

**Females and Males of Reproductive Potential**

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

**Lactation**

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

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-844-217-6468 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of Prescribing Information, including boxed warning, on the following pages.

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer.
1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

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

2.2 Recommended Dosage: The recommended dosage of EXKIVITY is 180 mg orally once daily until disease progression or unacceptable toxicity.

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

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time.

If a dose is omitted, do not take an additional dose. Take the next dose as prescribed the following day.

2.3 Dosage Modifications for Adverse Reactions: EXKIVITY dose reduction levels for adverse reactions are summarized in Table 1.

Table 1: Recommended EXKIVITY Dose Reductions

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

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

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc Interval Prolongation and Torsades de Pointes [see Warnings and Precautions (5.1)]</td>
<td>Grade 2 (QTc interval 481-500 msec)</td>
<td>First Occurrence</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (QTc interval &gt;501 msec or QTc interval increase of &gt;60 msec from baseline)</td>
<td>First Occurrence</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (Torsades de Pointes: polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)</td>
<td>First Occurrence</td>
</tr>
<tr>
<td>Interstitial Lung Disease (ILD)/pneumonitis [see Warnings and Precautions (5.2)]</td>
<td>Any grade</td>
<td>First Occurrence</td>
</tr>
</tbody>
</table>

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions (cont’d)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Ejection Fraction [see Warnings and Precautions (5.3)]</td>
<td>Grade 2 decreased ejection fraction</td>
<td>Withhold EXKIVITY until ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 decreased ejection fraction</td>
<td>Withhold EXKIVITY until ≤ Grade 1.</td>
</tr>
<tr>
<td>Diarrhea [see Warnings and Precautions (5.4)]</td>
<td>Intolerable or recurrent Grade 2 or Grade 3</td>
<td>Withhold EXKIVITY until ≤ Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Withhold EXKIVITY until ≤ Grade 1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume EXKIVITY at the same dose of the next lower dose.</td>
</tr>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (8.1)]</td>
<td>Recurrence</td>
<td>Permanent discontinuation EXKIVITY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ULN = upper limit of normal

* Graded per Common Terminology Criteria for Adverse Events Version 5.0

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

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

5 WARNINGS AND PRECAUTIONS

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

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

5.2 Interstitial Lung Disease (ILD)/Pneumonitis: EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (8.1)], 4.3% of patients including 0.9% Grade 3 events and 1.2% fatal events occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with a baseline QTc interval <470 msec.

Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT syndrome, heart disease, or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY [see Drug Interactions (7.1)], which may further prolong the QTc [see Drug Interactions (7.3)]. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the QTc prolongation [see Dosage and Administration (2.3)].

5.3 Cardiac Toxicity: EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population [see Adverse Reactions (8.1)], heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one other (0.4%) fatal case of heart failure. EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes [see Warnings and Precautions (5.1)].
The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 with EGFR exon 20 insertion mutation–positive locally advanced or metastatic NSCLC from Study AP32788-15-101, and patients with other solid tumors. Forty-eight percent (48%) were exposed for 6 months or longer and 12% were exposed for greater than one year. The most common (>20%) adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population [see Adverse Reactions (6.1)] diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days but diarrhea has occurred within 24 hours after administration of EXKIVITY. In 46% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake.

Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity [see Dosage and Administration (2.3)].

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

6 ADVERSE REACTIONS

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

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

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

The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 with EGR exon 20 insertion mutation–positive locally advanced or metastatic NSCLC who received prior platinum-based chemotherapy [see Clinical Studies (14)] Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment, significant, uncontrolled, active interstitial lung disease, or uncontrolled active cardiovascular disease, or prolonged QTc interval were excluded from enrollment in this trial. A total of 114 patients received EXKIVITY 180 mg once daily until disease progression or unacceptable toxicity; 86% were exposed for 6 months or longer and 14% were exposed for greater than 1 year.

Serious adverse reactions occurred in 48% of patients who received EXKIVITY. Serious adverse reactions in ≥2% of patients included diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. Fatal adverse reactions occurred in 1.8% of patients who received EXKIVITY, including cardiac failure (0.9%), and pneumonitis (0.9%). Permanent discontinuation occurred in 17% of patients who received EXKIVITY. Adverse reactions requiring permanent discontinuation of EXKIVITY in at least ≥2% of patients included diarrhea and nausea.

Dosage interruptions of EXKIVITY due to an adverse reaction occurred in 51% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included diarrhea, nausea and vomiting.

Dose reductions of EXKIVITY due to an adverse reaction occurred in 25% of patients. The adverse reaction requiring dose reduction in ≥5% of patients was diarrhea.

Table 3 summarizes the adverse reactions in Study AP32788-15-101.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXKIVITY (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades* (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>92</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>46</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>15</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
</tr>
</tbody>
</table>

** Events of Grade 3 only (no Grade 4 occurred).

- ** Rash includes angioedema, urticaria, and pruritus.
- ** Diarrhea includes abdominal pain, diarrhea, and vomiting.
- ** Nausea includes nausea, vomiting, and abdominal pain.
- ** Headache includes headache, and anxiety.
- ** Respiratory, Thoracic and Mediastinal Disorders includes cough, pharyngitis, and sinusitis.
- ** Cardiac Disorders includes atrial fibrillation, ventricular tachycardia, and pericarditis.
- ** Gastrointestinal Disorders includes abdominal pain, nausea, vomiting, and diarrhea.
- ** General Disorders and Administration Site Conditions includes fever, myalgia, and asthenia.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY** (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades* (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased red blood cells</td>
<td>59</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>25</td>
</tr>
</tbody>
</table>
In an embryo-fetal development study, once-daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose). Adverse effects on embryo-fetal development at this dose level included embryolethality due to post-implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high-dose level (10 mg/kg).

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

8.3 Females and Males of Reproductive Potential
EXKIVITY can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

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

8.5 Geriatric Use
Of the 114 patients [see Clinical Studies (14)] who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (39% vs 47%) and serious adverse reactions (64% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

8.6 Renal Impairment
No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
No dosage adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information). Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include diziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see Warnings and Precautions (5.1)].

17.1 QTc Interval Prolongation and torsades de Pointes
Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include diziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see Warnings and Precautions (5.1)].

17.2 Interstitial Lung Disease (ILD)/Pneumonitis
Inform patients of the risk of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain [see Warnings and Precautions (5.2)].

17.3 Cardiac Toxicity
Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see Warnings and Precautions (5.3)].

17.4 Diarrhea
Inform patients that EXKIVITY may cause diarrhea, which may be severe in some cases and should be treated promptly. Advise patients to have antidiarrheal medicine readily available and promptly start antidiarrheal treatment (e.g., loperamide), increase oral fluids and electrolyte intake, and contact their healthcare provider if diarrhea occurs [see Warnings and Precautions (5.4)].

17.5 Embryo-Fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5)].

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

17.7 Drug Interactions
Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)]. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

17.8 Missed Dose
Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day [see Dosage and Administration (2.2)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology (12.1)], EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryolethality (embryo-fetal death) and maternal toxicity at plasma exposures approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose [see Data]. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
In an embryo-fetal development study, once-daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose). Adverse effects on embryo-fetal development at this dose level included 

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY**</th>
<th>N (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>52</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>29</td>
<td>5.3</td>
</tr>
<tr>
<td>Increased alkaline phosphate</td>
<td>25</td>
<td>1.8</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>23</td>
<td>1.8</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>23</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>22</td>
<td>2.7</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>21</td>
<td>1.8</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>20</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* Grades per NCI CTCAE v5.0
** The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from baseline.
A Primer on the Rising Use of Medical Cannabis in Oncology

by ELOISE THEISEN, MSN, AGPCNP-BC

UNSURPRISINGLY, THE USE OF cannabis in patients with cancer appears to be increasing as more and more states are adopting cannabis legislation, both for medical and adult use. As of October, 36 states along with the District of Columbia have legalized medical cannabis, and 19 states plus the District of Columbia have legalized adult-use cannabis.¹

Furthermore, 7 states are expected to have adult-use cannabis legislation on the ballot in 2021, which could mean more than half of the United States supports adult use. In addition to increased cannabis legalization, there has been an explosion of cannabidiol and other nonimpairing cannabinoids that hit the market—thanks to the 2018 Farm Bill, which descheduled hemp. With nearly two-thirds of the states allowing for medical cannabis use and the legalization of hemp, accessing cannabinoids has become much easier, especially for patients with cancer, which is a qualifying condition in almost every state. The increased access to cannabinoids has led to patients’ curiosity. Many of these patients are seeking symptom relief with cannabis and are turning to their oncology care team for further guidance.

Yet, many oncology professionals have had little to no education on cannabis. In survey findings published in the Journal of Clinical Oncology in 2018, 70% of medical oncologists felt unequipped to make clinical cannabis recommendations, and 46% of oncologists are recommending cannabis for symptom relief even though they have had no formal training.² Additionally, an estimated 20% to 40% of patients with cancer are consuming some form of cannabis either during or after treatment—and that number may be underreported in states where cannabis is not legal.³

CANNABIS RESEARCH IN ONCOLOGY

Uncertainty exists among the different types of cannabis and whether clinical evidence supports cannabis use in certain medical conditions. Research is limited due to the federal designation of cannabis as a Schedule 1 drug.

Despite this restriction, there is sufficient evidence in some areas to demonstrate that cannabinoids may have a therapeutic effect. In 2017, the National Academy of Sciences, Engineering, and Medicine released The Health Effects of Cannabis and Cannabinoids report, which followed a review of more than 10,000 peer-reviewed journals. The authors concluded the following:¹

1. Conclusive evidence suggests that cannabis or cannabinoids are effective at treating chronic pain in adults with chemotherapy-induced nausea and vomiting.
2. Moderate evidence suggests that cannabis or cannabinoids are effective at improving short-term sleep disturbances, and limited evidence suggests effectiveness at improving appetite and decreasing weight loss.
3. There is insufficient evidence to demonstrate whether cannabis or cannabinoids are effective or ineffective in treating patients with gliomas or cancer-associated anorexia-cachexia.

Despite the comprehensive review of the literature, generalized anxiety disorder and chemotherapy-induced peripheral neuropathy were not addressed. However, the report highlighted the need for more clinical research to better understand the therapeutic effects of cannabinoids in certain diseases.

Even though limited data support the use of cannabis as a first-line treatment in cancer-related symptoms, many patients are using it to relieve anxiety, pain, nausea, vomiting, and insomnia. In a recent Cancer study, 42% of 612 patients with breast cancer reported using cannabis for symptom relief.³ Seventy-eight percent used it to help with pain, 70% for sleep, 57% for anxiety, and 46% for nausea and vomiting relief.

Data also found that 39% of patients discussed their cannabis use with their physicians and that when they did, it was initiated by the patient 76% of the time. Moreover, only 4% of respondents listed their physician as the most helpful source of information on cannabis, instead listing the internet (22%), family members (18%), and dispensary staff (12%) as a more helpful source of information. This trend is concerning, considering that the internet is not always an accurate or reliable source of information and that dispensary staff often have no medical background and little cannabis education.

Oncology professionals can start to address patient questions and concerns by educating themselves on the endocannabinoid system, cannabinoids, routes of administration, dosages, potential drug-drug interactions, adverse effects, and common cancer-related uses and considerations.

Unfortunately, this information is not widely taught in medical or nursing schools, and without standardized cannabis education, clinicians are self-selecting sources to decrease their knowledge gap. Foundational knowledge of key concepts can allow oncology professionals to better guide patients to safe and effective use.

THE ENDOCANNABINOID SYSTEM

Discovery of the first cannabinoid receptor in 1988 led to detection of the endocannabinoid system (ECS). The ECS, of which the main function is to maintain homeostasis, is a molecular signaling system that consists of 2 cannabinoid receptors (most commonly CB1 and CB2), ligands, and enzymes that normalize sleep, pain perception, memory, mood, and appetite. These receptors can be stimulated by human endogenous cannabinoids as well as plant-derived cannabinoids (phytocannabinoids) and synthetic cannabinoids.⁴

CB1 and CB2 are known as G protein-coupled receptors, and CB1 receptors are found predominantly in the adrenal glands, heart, kidneys, prostate, pancreas, colon, liver, central and peripheral nervous
systems, lungs, testes, and ovaries. Upon CB1 receptor activation, the CB1 receptors assist in relief from depression, anxiety and stress, pain and inflammation, neurodegenerative disorders, posttraumatic stress, and multiple sclerosis-related symptoms.6

CB2 receptors are also detected in the brain and peripheral nervous systems. However, these are mostly contained in the peripheral immune cells. These receptors are found in the brainstem neurons, lungs, microglia, and uterus. Upon activation, CB2 receptors are known to reduce inflammation and treat mental health disorders and neurologic diseases such as Alzheimer, Parkinson, Huntington, and multiple sclerosis.6

CANNABINOIDS
Cannabinoids are defined as chemical compounds, which can either be plant-derived (phytocannabinoids), synthetic, or endogenous, with the ability to influence the cannabinoid receptors while promoting neurotransmitter release. D-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are the 2 most commonly known cannabinoids, the first of which is primarily responsible for the euphoric effects of cannabis. Behavior, consciousness, mood, and perception are all altered by Δ-9 THC, which binds to CB1 receptors in the brain and causes a change to the function of the binding cell. Studies have suggested efficacy when using Δ-9 THC to treat the following conditions5-18:

- Nausea
- Pain
- Appetite loss
- Insomnia
- Sleep apnea
- Anxiety
- Inflammation
- Posttraumatic stress disorder

CBD is typically the second most abundant cannabinoid in cannabis. It is psychoactive but not in the same manner as THC. It can alter mood, perception, and decrease anxiety. Studies have suggested that CBD can also treat patients with the following conditions10-24:

- Nausea and vomiting
- Seizure disorders
- Psychosis disorders
- Inflammatory disorders
- Neurogenerative disorders
- Depression

THC and CBD can be found in the cannabis plant along with more than 100 other cannabinoids and can often be purchased through licensed dispensaries in legal states or through hemp retailers (online and in store). Phytocannabinoids are not standardized, and states can set their own limits on potency and testing. FDA pharmaceutical-grade THC is available via dronabinol, which is synthetic and has been approved an antiemetic and appetite stimulant. Cannabidiol (Epidiolex) is a medication that is derived from the cannabis plant and approved by the FDA as an anticonvulsant. In states where cannabis is legal for medical or adult use, patients can explore cannabinoids for a variety of health conditions without FDA approval.
CANNABIS ROUTES OF ADMINISTRATION

Cannabis products offer various routes of administration, including topical, transdermal, inhalation, sublingual, and ingestion. Understanding the onset and duration of action can be helpful in determining which route will effectively treat patient symptoms. Unfortunately, products’ availability to patients depends on an individual state’s cannabis laws, and many state cannabis programs severely limit the product and formulary options.

TOPICAL

Topical administration can provide localized relief within 15 minutes and often has little to no adverse effects (AEs). Upon activation, CB1 receptors on the skin assist in redness and inflammation reduction linked with conditions such as atopic and contact dermatitis and psoriasis. Evidence also suggests that topical cannabis can reduce arthritis-related pain and inflammation. There is little risk involved with this administration method.

TRANSDERMAL

Transdermal cannabis products—which are most commonly patches—are intended to penetrate the skin and reach the bloodstream and can provide between 6 and 12 hours of relief while avoiding first-pass metabolism. Transdermal products may be the optimal administration choice in patients whom drug interactions or medication adherence is a concern.

INHALATION

Inhalation provides relief quickly by reaching the bloodstream within minutes; this method is also found to be the most predictable while having the most control. It also provides a benefit for those who are unable to ingest other forms of medications. Chronic use has been associated with bronchitis and airway inflammation, so the benefit must outweigh the risk. Additionally, most indications for inhalation are short term.

INGESTION

Ingesting cannabis is a go-to choice for patients who suffer from chronic pain, inflammation, nausea, and insomnia because it can provide more durable and dependable relief. However, it does have variability in onset of action and is dependent on a patient’s metabolism, genetics, gender, and food intake. Taking these factors into consideration, the onset of action can range from 30 minutes to 2 hours or more.

That being said, the effects of ingesting cannabis can last for at least 5 hours. Due to this factor, patients can overconsume and experience AEs, such as tachycardia, paranoia, hypotension, vomiting, and hallucinations. AEs associated with cannabis use are often from ingestible products. The use of the “go low and slow” method can help avoid some unwanted AEs associated with cannabis overconsumption.

DRUG INTERACTIONS

Although drug interactions with cannabis are rarely hazardous, there is still potential for interactions to occur, especially with ingested cannabinoids.

When taken orally, cannabinoids are metabolized by the CYP family of enzymes. THC is often metabolized by the CYP2C9, CYP2C19, and CYP3A4 enzymes, which convert THC into 11-hydroxy-THC. CBD, however, is commonly metabolized by the CYP2C19 and CYP3A4 enzymes, which convert CBD into 7-hydroxy-cannabidiol.25,26 Because most medications are metabolized by CYP3A4, CBD and THC can inhibit or induce other medications metabolized through that same enzyme. Warfarin, among other medications, can inhibit or induce THC and CBD, which increases or decreases cannabinoid plasma levels.57

Cannabis should be used with caution with other central nervous system depressants, including alcohol, since it can generate sedative effects.

DOsing

Cannabis dosing remains one of the most challenging components of providing care. Very few clinical trials have established dosing protocols with cannabinoids for specific conditions. As it stands, most dosing protocols have been developed from real-world evidence rather than evidence-based trials. The go-low-and-slow method is most applicable with cannabis. Because cannabinoids can have biphasic effects, a low dose is often all a patient needs to achieve symptom relief.

CONSIDERATIONS FOR PATIENTS WITH CANCER

With cannabis accessibility on the rise, many patients with cancer will be seeking guidance on the safe and effective use for symptom management. As cannabis research evolves and the industry matures, oncology professionals can look to cannabinoids as a potential supportive medicine. With proper guidance, cannabis can have a high safety profile with adverse effects that are generally well tolerated when administered at low doses. Patients are using it. Therefore, oncology professionals must be ready to meet the needs of their patients.
COVID-19 Pandemic Highlights Underrecognized Vulnerability of Patients With CLL

by JULIE E. CHANG, MD

AT THE ONSET OF the pandemic, hematology/oncology physicians were challenged in counseling patients with serious underlying malignant conditions about their risk for severe disease due to COVID-19. Certain patient populations were at greater risk than others, such as those who recently underwent allogeneic bone marrow transplant; however, the danger to other high-risk populations was opaquer. Emerging data identify the unique risks that patients with chronic lymphocytic leukemia (CLL) face across all stages of the disease spectrum in the setting of COVID-19 exposure, specifically the reduced response to currently available vaccines. Given the sizable prevalence of CLL in the United States (estimated at 195,129 cases in 2018),¹ an understanding of these risks is important to optimally educate and treat patients with CLL as the pandemic remains a formidable threat with deaths exceeding 3 million worldwide.²

Clinicians have long known about the innate immune defects associated with CLL,³ and these arguably have never been highlighted more strongly than during the COVID-19 pandemic. Multiple abnormal cellular and humoral responses in CLL lead to defects in the immune response, including active COVID-19 infection and reduced response to vaccines.³⁴ Results from 2 large multicenter studies have demonstrated increased rates of more severe COVID-19 infection and mortality in patients with CLL.³⁶ One of these studies included 198 patients with CLL who received a diagnosis of COVID-19. Investigators found that rates of hospital and intensive care unit admissions, intubation, and mortality were similar in patients on active therapy compared with those being treated with observation or a “watch and wait” approach; the overall case mortality rate was approximately 30%.³ These data from the initial year of the pandemic were very sobering for physicians and patients.

In terms of COVID-19 response, investigators have observed that rates of seroconversion to measurable levels of antibodies against the COVID-19 spike protein are significantly lower for patients with CLL compared with patients with solid tumors and among those with other types of hematologic malignancies. For example, in a study (NCT04794387) sponsored by the Leukemia & Lymphoma Society, investigators evaluated outcomes for patients with hematologic malignancies treated with the full COVID-19 vaccine series of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna).⁷ Seropositivity to the spike protein was observed in 64.2% of patients with CLL compared with 95.1% of patients with multiple myeloma and 98.5% of patients with Hodgkin lymphoma (FIGURE 1⁷). The lowest rates of seroconversion to the vaccine were among patients with CLL treated with B-cell-depleting therapies: obinutuzumab (Gazyva; 18.1%), Bruton tyrosine kinase (BTK) inhibitors (42.9%-50%), and venetoclax (Vencexa; 39.3%) (FIGURE 2⁷).

Further, investigators reported low rates of seroconversion to the COVID-19 vaccine in a prospective Israeli study (NCT04746092) of 167 patients with CLL; the overall antibody response rate to vaccine was 39.5%.³ Low rates of antibody response to the vaccine in the setting were reported in patients treated with BTK inhibitors (16.0%) and venetoclax (13.6%), and were highest in patients

FIGURE 1. COVID-19 Vaccine Response in Hematologic Malignancies⁷

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL (n = 650)</td>
<td>35.8%</td>
<td>64.2%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>98.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>77.6%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Myeloma (n = 184)</td>
<td>91.5%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

CLL, chronic lymphocytic leukemia.
who obtained clinical remission after treatment (79.2%) and those who were previously untreated (55.2%).

Investigators at Roswell Park Comprehensive Cancer Center in Buffalo, New York, suggest that the ability to generate an antibody response to the COVID-19 vaccine may begin to improve by 9 months following completion of B-cell–depleting therapy for CLL. Retrospective data showed an improvement in antibody response from 11% in patients with active B-cell–directed therapy within 9 months of vaccination to 88% in patients who received no prior treatment or whose treatment was last administered more than 9 months prior to vaccination.

These data must be interpreted through the lens of rapidly evolving clinical experience as the COVID-19 pandemic continues. Rates of seroconversion are lower for patients with CLL regardless of their treatment or remission status.

As we navigate this rapidly changing landscape, it is helpful to have some guiding principles for the treatment of patients with CLL:

- Given the higher rates of vaccine antibody response in the absence of recent B-cell-depleting therapy, counsel patients to complete a COVID-19 vaccination series prior to initiation therapy (ie, BTK inhibitors, venetoclax, monoclonal antibody therapy).

The measurement of antibody response to the COVID-19 spike protein is a single measure of humoral response and does not account for the T-cell response and the remainder of the complex immune cascade. Therefore, low or negative COVID-19 antibodies should not discourage the recommendation for a third COVID-19 vaccination dose (with BNT162b2 or mRNA-1273) or the recommendation for CLL patients at risk of not generating a measurable antibody response to receive vaccination.

Data concerning increased risk for severe COVID-19 infection and lower rates of protection from infection with the COVID-19 vaccine are compelling and relevant talking points in educating patients and families about the importance of maintaining appropriate precautions after completing a COVID-19 vaccination series.

Given the lower rates of seroconversion among vaccinated patients with CLL, it is important to counsel patients on the importance of COVID-19 testing if symptoms develop or documented COVID-19 exposure to allow for possible administration of casirivimab and imdevimab (REGEN-COV [Regeneron]) early in the disease course.

These data and recommendations will evolve as the pandemic continues. As clinicians, we are tasked with educating ourselves and our patients on these emerging data. It is critical to be mindful of managing risks present among our most vulnerable populations, which includes all individuals with CLL regardless of their treatment or remission status.

**REFERENCES**


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**FIGURE 2. COVID-19 Vaccine Seroconversion With Active CLL Therapies**

<table>
<thead>
<tr>
<th>BCL2 inhibitors</th>
<th>Venetoclax 39.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK inhibitors</td>
<td>Ibrutinib 48.6%</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>42.9%</td>
</tr>
<tr>
<td>Monoclonal</td>
<td>Rituximab 44.0%</td>
</tr>
<tr>
<td>B-cell therapy</td>
<td>Obinutuzumab 18.1%</td>
</tr>
</tbody>
</table>

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia.
**New Players Join Quest for a Therapeutic Foothold Against TGFβ**

*by JANE DE LARTIGUE, PhD*

**BINTRAFUSP ALFA, A NOVEL FUSION** protein designed to target the transforming growth factor beta (TGFβ) pathway, racked up 3 clinical trial disappointments in less than a year, leaving the future of its development in question.1,2 It is one of a plethora of agents designed to target the TGFβ network that have come and gone from clinical development in the oncology field during the past 15 years.3-5

None of the TGFβ-targeting agents has gained approval for cancer therapy. However, the challenges have not stopped investigators from continuing to pursue TGFβ signaling as a therapeutic target, and novel drugs continue to enter clinical development as investigators delve more deeply into the complexities of TGFβ signaling in healthy and cancerous cells (TABLE). In recent years, the immunoregulatory functions of TGFβ signaling have received significant interest, particularly its potential role in resistance to immune checkpoint inhibitors (ICIs) (FIGURE). Study findings have suggested that high levels of TGFβ in the tumor microenvironment correlate with lower response rates to ICIs and that TGFβ pathway inhibition could synergize with PD-L1/PD-L1 pathway inhibition.6,7 Fusion proteins such as bintrafusp alfa, which also targets PD-L1,19 is designed to block the immunosuppressive effects of TGFβ, represent just one of numerous drug designs directed at TGFβ that have been evaluated in clinical trials. Ongoing programs are evaluating monoclonal antibodies targeting the TGFβ ligands and small-molecule inhibitors of the TGFβ receptors (TGFβRs), in addition to vaccines and other strategies.3,5

Drug development has been frequently hindered by dose-limiting toxicities (DLTs) or limited clinical efficacy owing in large part to the high level of plasticity and complexity in TGFβ signaling and its apparent dual role as tumor suppressor and oncogenic activator during tumor development and progression.

Notably, TGFβ signaling plays an important role in the development of the cardiovascular system, in normal cardiac function, and in remodeling cardiac tissue after injury, and TGFβ inhibition is associated with a risk of cardiac toxicity.1,4 In particular, small-molecule inhibitors of TGFβRI have been shown in animal studies to be associated with dose-dependent serious cardiovascular adverse events.10,11

**SMALL-MOLECULE INHIBITORS**

To date, the most widely studied agents targeting this pathway are 2 small-molecule TGFβRI inhibitors: galunisertib (LY2157299), developed by Eli Lilly and Company, and vactosertib (TEW-7197), developed by MedPacto. In phase 1 clinical trials, galunisertib demonstrated good tolerability and some antitumor activity in various patient populations, including patients with metastatic pancreatic cancer, glioma, and hepatocellular carcinoma (HCC).4,5,12 Phase 2 studies yielded mixed results; the combination of galunisertib and sorafenib (Nexavar) in patients with advanced HCC demonstrated prolonged overall survival (OS), but the combination of galunisertib and lomustine in recurrent glioblastoma did not.4,5,12 Ongoing clinical development of galunisertib is unclear;

**TABLE. Clinical Development of Drugs Targeting TGFβ Signaling**

<table>
<thead>
<tr>
<th>Drug/developer</th>
<th>Cancer types</th>
<th>Most advanced development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small-molecule inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galunisertib (LY2157299)/Eli Lilly and Company</td>
<td>mCRPC, rectal adenocarcinoma, nasopharyngeal carcinoma, recurrent GBM</td>
<td>2</td>
</tr>
<tr>
<td>Vactosertib (TEW-7197)/MedPacto</td>
<td>Urothelial carcinoma, NSCLC gastric cancer, CRC with liver metastases, desmoid tumors</td>
<td>2</td>
</tr>
<tr>
<td>PF-06952229/Pfizer</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAR439459/Sanofi</td>
<td>Multiple myeloma, liver cancer</td>
<td>1/2</td>
</tr>
<tr>
<td>NIS793/Novartis</td>
<td>Pancreatic ductal adenocarcinoma</td>
<td>3</td>
</tr>
<tr>
<td>ABBV-151/AbbVie</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>SRK-181/Scholar Rock</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fusion proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bintrafusp alfa/Merck KGaA</td>
<td>NPC, malignant pleural mesothelioma, BTC, HNSCC, NSCLC, sarcoma, TNBC, urothelial cancer, neuroblastoma, thymic cancer, esophageal cancer prostate cancer, gastric cancer, CRC</td>
<td>2</td>
</tr>
<tr>
<td>AVID200 (BMS-986416)/Bristol Myers Squibb</td>
<td>Myelofibrosis, advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>SHR-1701/Jiangsu HengRui Medicine Co, Ltd</td>
<td>CRC, gastric/gastroesophageal cancer</td>
<td>3</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemogenovatucel-T (Vigil/FANG)/Gradalis</td>
<td>Ewing sarcoma</td>
<td>3</td>
</tr>
</tbody>
</table>

BTC, biliary tract cancer; CRC, colorectal cancer; GBM, glioblastoma; HNSCC, head and neck squamous cell carcinoma; mCRPC, metastatic castration-resistant prostate cancer; NPC, nasopharyngeal cancer; NSCLC, non–small cell lung cancer; TGFβR, transforming growth factor beta receptor; TNBC, triple-negative breast cancer.

*Trials are listed on ClinicalTrials.gov. Some studies are active but no longer enrolling participants or have not yet begun recruiting patients.
it is no longer included in the Eli Lilly pipeline, but there are several ongoing clinical trials in metastatic castration-resistant prostate cancer (NCT02452008) and rectal cancer (NCT02688712; EXIST) sponsored by the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Providence Health & Services, respectively, with Eli Lilly listed as collaborator.

Several clinical trials have demonstrated responses and a tolerable safety profile for vactosertib in combination with PD-L1/PD-L1 ICIs in patients with colorectal cancer (CRC) and non–small cell lung cancer (NSCLC) and with pomalidomide (Pomalyst) in multiple myeloma.

Results from 2 small studies in patients with desmoid tumors and gastric adenocarcinoma were recently reported. In a phase 1/2 study (NCT03802084), 7 patients with advanced desmoid tumors were treated with 100 mg or 200 mg vactosertib twice daily on a schedule of 5 days on, 2 days off in combination with imatinib (Gleevec) 400 mg once daily. There were 2 partial responses (PRs) and 2 patients with stable disease (SD) at the 100-mg dose and 3 patients with SD at the 200-mg dose. In another phase 1/2 study (NCT03698825) a schedule of 5 days on, 2 days off also was applied to twice-daily vactosertib (NCT03698825) a schedule of 5 days on, 2 days off in combination with paclitaxel (80 mg/m²). At 12 weeks, the overall response rate (ORR) was 16.7% and the disease control rate (DCR) was 83.3%. No DLTs or cardiac toxicity were observed in either trial.

**MONOCLONAL ANTIBODIES**

Several monoclonal antibodies directed at TGFβ are in clinical development, including pan-TGFβ antibodies that target all 3 isoforms of TGFβ (TGFβ1, 2, and 3) and others that are isoform specific. Sanofi is developing SAR439459, a fully human pan-TGFβ antibody. A phase 1 first-in-human (FIH) study (NCT03192345) testing SAR439459 as monotherapy and in combination with the PD-1 inhibitor cemiplimab-rwlc (Libtayo) is ongoing. In addition, phase 1/2 studies evaluating the agent in various combinations are underway in multiple myeloma (NCT04643002) and liver cancer (NCT04524871).

Data from the dose-escalation part of the FIH study were reported at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting. In part A, SAR439459 was administered over 6 dosing levels ranging from 0.05 to 15 mg/kg as monotherapy every 2 weeks. In part B, monotherapy dose levels cleared in dose escalation were administered in combination with a fixed dose of cemiplimab. As of January 2020, 28 patients had been enrolled to part A and 24 to part B.

In part A, 6 patients had best response of SD, there were 2 DLTs in 8 evaluable patients at dose level 4 (3 mg/kg). In part B, 2 patients had best response of SD and 1 of 6 evaluable patients experienced DLTs with SAR439459 at dose level 5 (22 mg/kg) plus 350 mg of cemiplimab. Maximum-tolerated dose was not reached in either part. Patients continue to be enrolled to dose expansion.

NIS793, which Novartis is developing, is another fully human pan-TGFβ antibody. Results from a phase 1b study (NCT02947165) of NIS793 as monotherapy and in combination with the PD-1 inhibitor spartalizumab (PDR001) in patients with advanced solid tumors were presented at the 2021 ASCO meeting.

Patients were initially treated with NIS793 monotherapy at doses ranging from 0.3 to 1 mg/kg every 3 weeks. Dose escalation continued in combination with spartalizumab (0.3-30 mg/kg NIS793 once every 3 weeks plus 300 mg spartalizumab once every 3 weeks or 20-30 mg/kg NIS793 once every 2 weeks plus 400 mg spartalizumab once every 4 weeks). In dose-expansion cohorts, patients with either NSCLC that was resistant to prior anti-PD-1/PD-L1 therapy (n = 20) or microsatellite-stable CRC (n = 40) were treated with 30 mg/kg NIS793 plus 300 mg spartalizumab every 3 weeks. During dose escalation of the combination, 2 patients achieved PR, 1 with clear cell renal cell carcinoma and 1 with NSCLC, while during dose expansion there were 2 PRs among patients with CRC.

The ability of TGFβ to modulate the tumor microenvironment may be particularly important in pancreatic cancer, in which the tumor is often surrounded by dense fibrotic stroma that can impede drug delivery. NIS793, which may reduce fibrosis by inhibiting TGFβ signaling, recently received an orphan drug designation in combination with standard chemotherapy for the treatment of patients with pancreatic cancer. The phase 2 daNIS-1 trial (NCT04390763) is evaluating the combination of NIS793 and standard chemotherapy, with or without spartalizumab, in the frontline treatment of patients with metastatic pancreatic ductal adenocarcinoma. A similar phase 3 trial (NCT04935359) in this setting, but without a spartalizumab arm, also is enrolling patients.

Meanwhile, Boston-based pharmaceutical company Scholar Rock is developing SRK-181, a monoclonal antibody designed to specifically inhibit activation of the latent (inactive precursor) form of TGFβ1, but not latent TGFβ2 or TGFβ3 or the active form of any of these proteins. In the recently initiated FIH DRAGON trial (NCT04291079), SRK-181 is being evaluated as monotherapy and in combination with PD-L1 inhibitors in patients with advanced solid tumors. The GARP protein (also called LRRC32) binds to latent TGFβ1 on the surface of regulatory T cells and platelets, and this complex

![FIGURE. Immune Cell Populations Regulated by TGFβ](https://example.com/immune_cell_populations.png)
THE TRANSFORMING GROWTH FACTOR beta (TGFβ) superfamily comprises a group of more than 30 related proteins. First described in the late 1970s, the namesake member of this family is represented by 3 isoforms in mammalian cells—TGFβ1, TGFβ2, and TGFβ3—which share significant similarity in their structures and functions despite being differentially expressed across tissue types.

The TGFβ cytokines are secreted by several cell types and play essential roles in a wide array of cellular processes by binding to their receptors (TGFβRs) and activating intracellular signaling pathways.

Given its essential functions, TGFβ signaling is tightly regulated at multiple levels. Notably, TGFβ is synthesized as a propeptide consisting of 2 segments: the TGFβ peptide and latency-associated peptide (LAP). The propeptide homodimerizes and forms the small latent complex (SLC), in which the LAP shields the TGFβ peptide from receptor binding. The SLC then further binds to a latent TGFβ-binding protein to form the large latent complex (LLC). The LLC is secreted from the cell and becomes anchored to the extracellular matrix (ECM), where the latent TGFβ is maintained in an inactive state incapable of receptor binding.

To allow initiation of TGFβ pathway signaling, the latent TGFβ must be activated by being released from the ECM and dissociating from the LLC. Removal of LAP from TGFβ is a particularly critical step and can occur via a number of mechanisms, including exposure to certain cellular conditions (eg, pH or temperature changes), proteolytic cleavage (eg, by proteases), or interaction with integrins.

Active, mature TGFβ is now free to bind to the TGFβRs, transmembrane serine/threonine kinase receptors also comprising 3 isoforms in mammalian cells: TGFβRI, TGFβRII, and TGFβRIII. A TGFβ homodimer binds to a tetrameric receptor complex consisting of 2 TGFβRI and 2 TGFβRII units. The third TGFβ isoform, TGFβRIII (also known as betaglycan), can act as a coreceptor, facilitating interactions between TGFβs and TGFβRII. TGFβ2 is especially dependent on this function of TGFβRII for its signaling.

Ligand binding activates TGFβRI, causing it to phosphorylate TGFβRII at a highly conserved intracellular region enriched in glycine and serine amino acid residues. Thus activated, TGFβRI phosphorylates downstream targets to propagate the intracellular signaling cascade. Various pathways are triggered by TGFβR activation, with canonical TGFβ pathway signaling initiated when the downstream phosphorylation targets of TGFβRI are SMAD proteins, particularly SMAD2 and SMAD3 (FIGURE).

Upon phosphorylation by TGFβRI, SMAD2 and SMAD3 form a complex with the chaperone protein SMAD4, which facilitates translocation of the complex into the nucleus. There, the SMAD complex associates with sites in the genome known as SMAD-binding elements, consensus DNA sequences involved in regulating the expression of TGFβ target genes. TGFβ can also trigger noncanonical, SMAD-independent signal transduction, such as through the PI3K/AKT and MAPK pathways, and significant cross talk also occurs among canonical and noncanonical TGFβ-induced signaling pathways and other key signaling cascades.

TGFβ signaling has a highly complex, seemingly dual role in cancer. In healthy tissue and early tumorigenesis, TGFβ acts as a tumor suppressor, promoting the expression of genes that limit cellular proliferation and induce cell cycle arrest. However, mutations in certain TGFβ pathway components, which have been identified across many tumor types, accumulate as cancer progresses. The resultant loss of TGFβ signaling inhibition leads to upregulated expression of key transcriptional targets of the canonical TGFβ pathway involved in tumor development and progression.

REFERENCES

The Network

TGFβ Signaling Casts a Wide Net

FIGURE. Main Elements of TGFβ Signaling

This figure illustrates the multiple steps in canonical signaling of the transforming growth factor beta (TGF) network. TGF receptor II (TGFRII) recruits and phosphorylates TGFRI, stimulating the formulation of complexes with SMAD4 proteins. SMAD7 participates in a negative feedback loop to regulate the duration and intensity of TGF signaling.
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regulates the bioavailability and secretion of TGFβ1. Another novel antibody, Abbvie’s ABBV-151, binds to the GARP-latent TGFβ1 complex and inhibits TGFβ1 release from the cell surface.25-27

**THERAPEUTIC VACCINES**

Several therapeutic cancer vaccines designed to prevent TGFβ synthesis and activation have been developed but clinical trials have yielded mixed results. NovaRx Corporation developed belagenpumatucel-L (Lucanix), a cancer vaccine composed of 4 irradiated human NSCLC cell lines transfected with a TGFβ2 antisense gene. The vaccine showed promise in patients with advanced NSCLC; however, in a phase 3 trial (NCT00676507) of belagenpumatucel-L compared with placebo as maintenance therapy for patients with advanced NSCLC treated with platinum-based chemotherapy, there was no significant difference in OS.3,4,9,12

Gemogenovatucel-T (Vigil; formerly known as FANG) is an autologous vaccine in which the tumor cells are transfected with a plasmid containing the granulocyte-macrophage colony-stimulating factor (GM-CSF; also called CSF2) gene and a short hairpin RNA targeting furin. The therapy, which Gradalis, Inc is developing, is designed to reduce the protein expression of furin, a protease involved in the processing of latent TGFβ1 and TGFβ2 into the active form.15,26,29

Investigators have carried out phase 2 clinical trials in several cancer types, including melanoma (NCT01453361) and CRC (NCT01505166), that were terminated for business reasons.26,28 Clinical development is ongoing, however, and results of the phase 2b VITAL trial (NCT02346747), in which gemogenovatucel-T was evaluated as frontline maintenance therapy in patients with ovarian cancer, were recently published.30

In the overall study population, median recurrence-free survival (RFS) was higher with the vaccine at 11.5 months (95% CI, 7.5-not reached) vs 8.4 months (95% CI, 7.9-15.5) with placebo but was not statistically significant (HR, 0.688; 90% CI, 0.44-1.07; P = .078). However, the vaccine showed greater efficacy in patients with wild-type *BRCA1/2* gene status (HR, 0.51; 90% CI, 0.30-0.88; P = .02).29 In the homologous recombination-proficient patients, median RFS was 10.6 months (95% CI, 5.9-not available) in the Vigil group vs 5.7 months (95% CI, 5.6-14.9) in the placebo group (HR, 0.386; 90% CI, 0.199-0.750; P = .007), according to a subgroup analysis presented at the 2021 ASCO meeting.31

Data from phase 1 and 2 clinical trials suggest that gemogenovatucel-T may have activity in combination with irinotecan and temozolomide in the treatment of patients with Ewing sarcoma.32,33 These data provided the rationale for the phase 3 VITA trial (NCT03495921) of this combination in patients with metastatic Ewing sarcoma with relapsed/refractory disease after 1 prior line of chemotherapy. This trial is ongoing but not actively recruiting participants, according to ClinicalTrials.gov.14

**FUSION PROTEINS**

In January 2021, bintrafusp alfa was one of the most notable TGFβ pathway–targeting agents in development. The fusion protein is composed of an antibody targeting PD-L1 fused to the extracellular domains of 2 TGFβRII molecules.3

Bintrafusp alfa has been evaluated in several tumor types; the agent elicited ORRs of approximately 20% across several studies in patients with advanced NSCLC and esophageal, gastric, and biliary tract cancers (BTCs).4,15-17 In patients with NSCLC, response rates were higher among patients with PD-L1–positive tumors (PD-L1 expressed by ≥ 1% of tumor cells; ORR, 36.0%), especially those with high PD-L1 levels (PD-L1 expressed by ≥ 80% of tumor cells; ORR, 85.7%).8 These data prompted progression into phase 2 and 3 clinical trials in NSCLC and BTC, but the results of these trials ultimately proved to be a source of significant disappointment for Merck KGaA and GlaxoSmithKline, the companies developing the drug. In January 2021, a review of data from the phase 3 INTR@PID Lung 037 trial (NCT03631706) in first-line treatment of patients with NSCLC with high PD-L1 expression levels prompted the companies to discontinue the trial based on the recommendation of the independent data monitoring committee (IDMC), which felt that it was unlikely that the trial would meet the coprimary end point of improved progression-free survival.38

Then, in March 2021, topline data from the phase 2 INTR@PID BTC 047 trial (NCT03833661), which examined the safety and efficacy of second-line treatment with 1200 mg bintrafusp alfa administered once every 2 weeks to 159 patients with BTC, did not meet the predefined threshold for regulatory filing in this setting.39 Finally, in August 2021, Merck announced that it was discontinuing the phase 2/3 INTR@PID BTC 055 trial (NCT04066491) based on a review of the data conducted by the IDMC, which concluded the study was unlikely to meet its primary objective of improved OS.1

A month later, the 2 companies announced that they were ending their partnership involving bintrafusp alfa, a deal that once was valued at $4.2 billion, effective September 30.12 Merck, which retains control of the drug, said the company would use advanced analytics to examine the trove of clinical data generated by studies into the drug. “The important insights this program has yielded about the biology of TGFβ will inform the collective understanding of this pathway,” Merck said in a statement.40 Nearly 40 clinical trials evaluating bintrafusp alfa are ongoing or actively recruiting patients, including studies in cervical, breast, and prostate cancers, and NSCLC, according to ClinicalTrials.gov.

A second TGFβ-PD-L1 bifunctional fusion protein, SHR-1701, is being developed by a Chinese company, Jiangsu HengRui Medicine Co, Ltd. Preliminary results from a phase 1 trial (NCT03774979) in 24 patients with advanced NSCLC harboring *EGFR* mutations demonstrated an ORR of 16.7% (95% CI, 4.7%-37.4%) and a DCR of 50.0% (95% CI, 29.1%-70.9%) among patients treated with SHR-1701 at a dose of 3, 10, or 20 mg/kg every 3 weeks or 20 mg/kg every 2 weeks.41

AVID200, a fusion protein comprising TGFβR extracellular domains fused to a human Fc domain, also is in development. This “TGFβ ligand trap” selectively binds and neutralizes TGFβ1 and TGFβ3, enhancing antitumor immunity. It is hoped that not blocking TGFβ2 will reduce the risk of cardiovascular toxicity.3,42

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

For a full list of references, see the article at Onclive.com.
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MULTIPLE TARGETED THERAPIES INCLUDING antibody-drug conjugates, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies have been approved by the FDA over the past 2 years for patients with HER2-positive metastatic breast cancer.1 Without comparative sequencing data, clinicians rely on toxicity profiles, lines of prior therapy, and patient characteristics in considering optimal treatments.

Specifically, investigators have reported improved outcomes with several therapies, even in the setting of heavily pretreated metastatic tumors and brain metastases. “The brain is a common site for metastases in HER2-positive disease,” Lee S. Schwartzberg, MD, FACP, said during a recent OncLive Peer Exchange®. “There are population-based studies that suggest that metastases occur at diagnosis in a fraction of patients, but clearly, as you go further on in the lines of therapy, the brain becomes more at risk for being a new site of disease.”

Joining Schwartzberg were a panel of breast cancer experts, who shared their insights on 4 recently approved targeted therapies for patients with relapsed HER2-positive metastatic breast cancer: tucatinib (Tukysa), fam-trastuzumab deruxtecan-nxki (Enhertu), neratinib (Nerlynx), and margetuximab-cmkb (Margenza). In addition to discussing the data that led to these agents’ approval, they shared their insights on using the agents in clinical practice.

HER2CLIMB (NCT02614794) On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab (Herceptin) and capecitabine (Xeloda) for adult patients with advanced unresectable or metastatic HER2-positive breast cancer who have received at least 1 prior anti-HER2-based regimen in the metastatic setting.2 The approval was based on data from the randomized, phase 2 HER2CLIMB trial, in which investigators randomized 612 heavily pretreated patients 2:1 to receive tucatinib or placebo plus trastuzumab and capecitabine. Patients were previously treated with trastuzumab, pertuzumab (Perjeta), and ado-trastuzumab emtansine (T-DM1; Kadcyla).3

“Tucatinib is a TKI. It’s very HER2-specific and it doesn’t bind to the HER1 protein that well. It also binds tightly and doesn’t let go, so there’s some thought that once it’s bound, receptor-mediated endocytosis occurs and causes clearance of the receptor from the surface,” Vijayakrishna Gadi, MD, PhD, said.

HER2CLIMB showed that adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival (PFS) and overall survival (OS) compared with placebo.3 At 1 year, the PFS rate was 33.1% in the tucatinib arm vs 12.3% in the placebo arm (HR for disease progression or death, 0.54; 95% CI, 0.42-0.71; P < .001). The median PFS was 7.8 months vs 5.6 months, respectively. At 2 years, the OS rate was 44.9% in the tucatinib arm vs 31.4% in the placebo arm (HR for death, 0.68; 95% CI, 0.51-0.92; P = .016).

STATE-OF-THE-ART CARE FOR HER2+ METASTATIC BREAST CANCER

MODERATOR
Lisa A. Carey, MD, FASCO
Richardson and Marilyn Jacobs Preyer Distinguished Professor in Breast Cancer Research
Deputy Director, Clinical Sciences
University of North Carolina Lineberger Comprehensive Cancer Center
Chapel Hill, NC

PANELISTS
Vijayakrishna Gadi, MD, PhD
Professor and Director, Medical Oncology
University of Illinois College of Medicine
Associate Director, Translational Oncology
University of Illinois Cancer Center
Chicago, IL

Reshma Mahtani, DO
Associate Professor, Clinical Oncology
University of Miami Health System Sylvester Comprehensive Cancer Center
Miami, FL

Lee S. Schwartzberg, MD, FACP
Professor, Medicine
The University of Tennessee Health Science Center
Chief Medical Officer
OneOncology
Memphis, TN
arm vs 26.6% in the placebo arm (HR for death, 0.66; 95% CI, 0.50–0.88; P = .005), with a median OS of 21.9 months vs 17.4 months, respectively.

The panelists noted that HER2CLIMB has a unique trial design because it allowed patients with brain metastases were allowed to enroll. “Half the patients had brain metastases, and of the patients with the brain metastases, a large fraction had untreated and progressing brain metastases,” Gadi said. “This is the first study of a large size to randomize and [evaluate] such a patient cohort. It was a big risk in some regards, but the [investigators] were rewarded.”

Specifically, among the patients with brain metastases, the PFS rate at 1 year was 24.9% in the tucatinib arm compared with 0% in the placebo arm (HR, 0.48; 95% CI, 0.34–0.69; P < .001), with a median PFS of 7.6 months vs 5.4 months, respectively.

Crossover from the placebo arm to the tucatinib arm was permitted after the primary analysis. In an updated analysis with a median follow-up of 29.6 months, the OS and PFS benefit with tucatinib were maintained. The median OS was 24.7 months in the tucatinib arm vs 19.2 months in the placebo arm (HR, 0.73; 95% CI, 0.59–0.90; P = .004); the median PFS was 7.6 months vs 4.9 months, respectively (HR, 0.57; 95% CI, 0.47–0.70; P < .0001).

In an exploratory analysis of the 291 enrolled patients with brain metastases (198 in the tucatinib arm and 93 in the control arm), the addition of tucatinib to trastuzumab and capecitabine doubled the intracranial objective response rate (ORR; 47.3% vs 20.0%; P = .03). Tucatinib also reduced the risk of intracranial progression or death by 68% (HR, 0.32; 95% CI, 0.22–0.48; P < .0001) and the risk of death by almost 50% (HR, 0.58; 95% CI, 0.40–0.85; P = .005).5

“The study was, in my opinion, wildly positive. Not only did the median survivals push out—median OS, median PFS, etc—but they hit landmarks,” Gadi said. “When you follow those curves along the way and start looking at landmarks at 12 months, 18 months, etc, the curves stay apart and are meaningfully different at those time points. This seems like a not-so-gentle push, but some patients may see some long-term benefits from this.”

Overall, treatment with tucatinib was well tolerated, with a low rate of discontinuation due to adverse effects (AEs) and no new safety signals observed with longer follow-up.4 The most common AEs in the tucatinib arm included diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, and vomiting. Diarrhea and elevated aspartate transaminase levels of grade 3 or higher were more common in the tucatinib arm than in the placebo arm.

Based on positive data for tucatinib in heavily pretreated patients, the agent is under investigation in earlier settings. “There’s a trial that the Alliance for Clinical Trials in Oncology is running called CompassHER2 RD [NCT04457596], which is looking at adding tucatinib to T-DM1 in patients with residual disease after neoadjuvant therapy. That trial is open and enrolling now,” Lisa A. Carey, MD, FASCO, said.

DESTINY-BREAST01 (NCT03248492)
On December 20, 2019, the FDA granted accelerated approval to trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer who received at least 2 previous anti-HER2-based regimens in the metastatic setting.6 The approval was based findings from the open-label, single-group, multicenter, phase 2 DESTINY-Breast01 study, which evaluated trastuzumab deruxtecan in 184 heavily pretreated adults with pathologically documented HER2-positive metastatic breast cancer who had previously received T-DM1.7 Trastuzumab deruxtecan is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase 1 inhibitor.

In the intention-to-treat analysis, after a median follow-up of 11.1 months (range, 0.7–19.9 months), investigators observed a response to therapy in 112 patients (60.9%; 95% CI, 53.4–68.0%). The median duration of response was

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab deruxtecan (n = 184)*</th>
<th>T-DM1 (n = 263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>19.4 (14.1–NE)</td>
<td>6.8 (5.6–8.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>24.6 (23.1–NE)</td>
<td>NE</td>
</tr>
<tr>
<td>12-month OS rate (95% CI)</td>
<td>85% (79%–90%)</td>
<td>34.1% (27.7%–40.5%)</td>
</tr>
<tr>
<td>18-month OS rate (95% CI)</td>
<td>74% (67%–80%)</td>
<td>NE</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>61.4% (54.0%–68.5%)</td>
<td>NE</td>
</tr>
<tr>
<td>CR</td>
<td>6.5%</td>
<td>NE</td>
</tr>
<tr>
<td>PR</td>
<td>54.9%</td>
<td>NE</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>20.8 (15.0–NE)</td>
<td>NE</td>
</tr>
</tbody>
</table>

DESTINY-Breast03 (NCT03529110): phase 3 randomized, open-label study of T-DM1 vs trastuzumab deruxtecan in patients previously treated with trastuzumab and a taxane for HER2-positive metastatic breast cancer

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab deruxtecan (n = 261)</th>
<th>T-DM1 (n = 263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>16.8 (14.2–NE)</td>
<td>6.8 (5.6–8.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>24.4 (23.1–NE)</td>
<td>NE</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>61.4% (54.0%–68.5%)</td>
<td>34.1% (27.7%–40.5%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>20.8 (15.0–NE)</td>
<td>NE</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; NE, not estimated; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

*Updated analysis as of June 8, 2020.
Despite its toxicity risks, trastuzumab deruxtecan is making progress moving to earlier treatment lines. On October 4, 2021, the FDA granted this agent a breakthrough therapy designation for patients with HER2-positive metastatic breast cancer treated who have received at least 1 prior anti-HER2-based regimen. This designation was based on data from DESTINY-Breast03 (NCT03529110), which showed a highly statistically significant and clinically meaningful improvement in PFS with trastuzumab deruxtecan vs T-DM1 in patients previously treated with trastuzumab and a taxane for HER2-positive metastatic breast cancer (TABLE 1). According to data from the first head-to-head trial of the antibody-drug conjugate, the median PFS for patients treated with trastuzumab deruxtecan was not reached (95% CI, 18.5-not estimable [NE]) vs 6.8 months (95% CI, 5.6-8.2) with T-DM1 (HR, 0.28; 95% CI, 0.22-0.37; \( P = 7.8 \times 10^{-23} \)). Among the 261 patients in the trastuzumab deruxtecan arm the 12-month PFS rate was 75.8% (95% CI, 69.8%-80.7%) vs 34.1% (95% CI, 27.7%-40.5%) among the 263 patients treated in the T-DM1 arm. The median OS was NE in both arms (HR, 0.56; 95% CI, 0.36-0.86; \( P = 0.00712 \)). The 12-month OS rates were 94.1% (95% CI, 90.3%-96.4%) vs 85.9% (95% CI, 80.9%-89.7%), respectively.

**NALA (NCT01808573)**

On February 25, 2020, the FDA approved neratinib in combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer who have received at least 2 prior anti-HER2-based regimens in the metastatic setting. The agency granted approval based on data from the randomized phase 3 NALA trial, which compared neratinib plus capecitabine with lapatinib (Tykerb) plus capecitabine, the previous standard of care, in 621 patients. The study included patients with asymptomatic central nervous system (CNS) disease.

“Neratinib, another TKI, [it’s] different from tucatinib in the sense that it’s [an irreversible] pan-HER TKI, it’s slightly older, and it was released earlier,” Schwartzberg said. In contrast, lapatinib is a reversible dual TKI. Patients in the neratinib arm showed significantly improved PFS (HR, 0.76; 95% CI, 0.63-0.93; stratified log-rank \( P = 0.0059 \)), which Schwartzberg said amounted to an approximate 2.2-month improvement. The ORR was 32.8% in the neratinib arm and 26.7% in the lapatinib arm, with a median duration of response of 8.5 months vs 5.6 months, respectively. Fewer interventions for CNS disease occurred in the neratinib arm than in the lapatinib arm (cumulative incidence, 22.8% vs 29.2%; \( P = .043 \)).

Overall, neratinib was well tolerated. The most common all-grade AEs included diarrhea (83% in the neratinib arm vs 66% in the lapatinib arm) and nausea (53% vs 42%, respectively). Treatment discontinuation rates were similar between the groups.

“There are 2 new, active regimens that we see with tucatinib and trastuzumab deruxtecan,” Schwartzberg said. “In my mind, the neratinib-capecitabine would come afterward. It might be considered for fourth-line therapy, particularly in a patient who had previous exposure to a TKI and showed benefit.”

**SOPHIA (NCT02492711)**

On December 16, 2020, the FDA approved margetuximab in combination with chemotherapy for adult patients with metastatic HER2-positive breast cancer who have received at least 2 prior anti-HER2 regimens, at least 1 of which was for metastatic disease. The agency’s decision was based on results from the SOPHIA trial, which randomly assigned 536 patients with pretreated HER2-positive advanced breast cancer to receive margetuximab plus chemotherapy (n = 266) or trastuzumab plus chemotherapy (n = 270).

Margetuximab is a fragment crystallizable (Fc)-engineered, immune-activating, HER2-directed monoclonal antibody. “What’s interesting about margetuximab is that it may be the first of other drugs in this class [for which] we’re not looking at combining a chemotherapy through an ADC gene, such as trastuzumab deruxtecan, but there’s engineering of the intrinsic antibody molecule,” Schwartzberg said. “Margetuximab differs from trastuzumab because the Fc region of the antibody was engineered to increase allele activity, which the margetuximab binds to.”
Updated data for SOPHIA showed that margetuximab elicited a median PFS of 5.8 months vs 4.9 months with placebo (HR, 0.76; 95% CI, 0.59-0.98; P = .033).14 The confirmed ORR was 22% in the margetuximab arm vs 16% in the trastuzumab arm, with a median duration of response of 6.1 months and 6.0 months, respectively. An exploratory PFS analysis by CD16A genotype suggested that the presence of a CD16A-158F allele may predict margetuximab benefit over trastuzumab. In the SOPHIA trial, patients who were homozygous for the CD16A-158VV allele (15% of participants) received no benefit from margetuximab. “The different magnitude of benefit among the different alleles is interesting. I was surprised that [margetuximab] wasn’t approved based on any genotyping,” Mahtani said.

Schwartzberg said he would consider margetuximab as a fourth- or fifth-line choice for his patients with metastatic HER2-positive breast cancer, despite it being unclear whether the efficacy of this treatment might be affected by previous tucatinib or trastuzumab use. “We don’t have the data there, but we can extrapolate and say that because they’re novel agents, we can probably use them,” he said.

Carey said that the natural direction for margetuximab would be as a replacement for trastuzumab in patients with the low-affinity phenotype, as trastuzumab appears to be more efficacious in the setting of high-affinity alleles, but that the data to support this have yet to emerge. She noted that the Translational Breast Cancer Research Consortium’s phase 2 MARGOT trial (NCT04425018) will help guide the use of margetuximab.15 “[The trial is] directly comparing chemotherapy plus trastuzumab vs chemotherapy plus margetuximab, with a PCR [polymerase chain reaction] end point looking at the additional data, but only in low-affinity allele types,” she said. MARGOT is currently recruiting patients.

**REFERENCES**

MANIFEST 2

Evaluating the investigational BET inhibitor pelabresib (CPI-0610) + ruxolitinib in patients with myelofibrosis who are JAK-inhibitor naïve

A phase 3, global, randomized, double-blind trial of first-line treatment

Pelabresib is an investigational new drug and not yet approved by any regulatory authority

Study population
JAKi-naïve patients with symptomatic myelofibrosis requiring treatment

Prespecified subgroup analyses
Patients stratified by prognostic risk, platelet count, and spleen volume

Treatment arms
Pelabresib + ruxolitinib
Placebo + ruxolitinib

Double-blind randomization (1:1)

Open to JAKi-naïve patients with primary myelofibrosis (PMF), post-polycythemia vera MF (PPV-MF), or post-essential thrombocytopenia MF (PET-MF) and symptomatic disease, advanced MF requiring therapy, and splenomegaly.

BET=bromodomain and extra-terminal domain; JAK=Janus kinase; JAKi=JAK inhibitor.

Please visit manifestclinicaltrials.com or ClinicalTrials.gov for full trial information, including full eligibility criteria.

Learn more about opportunities for investigators and patient enrollment:
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Or contact manifest-2@constellationpharma.com

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