Clinical Trial Diversity Efforts Gain Steam

PEER EXCHANGE
Precision Medicine Alters CHOLANGIOCARCINOMA Landscape

Strategies for Targeting PI3K Proliferate

NEW YORK GU™ HIGHLIGHTS
Updates on Renal Cell Carcinoma and Prostate Cancer

THE TALK
Experts Put New MULTIPLE MYELOMA Triplets Into Context

CLINICAL PERSPECTIVES
Susan B. Kesmodel, MD, Discusses Lymphedema in BREAST CANCER
Jeffrey C. Goh, MBBS, FRACP, Describes Novel OVARIAN CANCER Doublet

MONTEFIORE EINSTEIN CENTER FOR CANCER CARE
Evolving Psychosocial Care Models Step Forward as the Next Targeted Cancer Therapy

By Alyson B. Moadel-Robblee, PhD
**In Relapsed or Refractory FLT3m+ AML,**

**XOSPATA Is the Only FDA-Approved Targeted Monotherapy to Deliver Superior Overall Survival** vs Salvage Chemotherapy

---

**36% reduced risk of death with XOSPATA (n=247)**

vs salvage chemotherapy (n=124)

HR=0.64 (95% CI: 0.49, 0.83); P=0.0004

---

**9.3 months median OS with XOSPATA (95% CI: 7.7, 10.7)**

vs 5.6 months with salvage chemotherapy

(95% CI: 4.7, 7.3)

---

**Gilbertinib (XOSPATA) sets a standard in relapsed or refractory FLT3m+ AML**

**Gilbertinib (XOSPATA) is the ONLY Category 1 recommendation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for patients with relapsed or refractory FLT3m+ AML**

---

**XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy regimen in adult patients with relapsed or refractory FLT3m+ AML.**

**Prespecified salvage chemotherapy regimens included high-intensity combinations MEC and FLAG-IDA and low-intensity regimens LDAC and AZA.**

---

**References:**


---

Scan the QR code to visit XospataHCP.com for more information
†The OS endpoint was measured from the date of randomization until death by any cause in the final analysis, which included 371 patients randomized 2:1 to receive XOSPATA or a FLT3-TKD mutation status.

¶AZA: azacitidine 75 mg/m² once daily by SC injection or IV infusion for 7 days.1

§FLAG-IDA: granulocyte colony-stimulating factor 300 mcg/m² once daily by SC injection Days 1 to 5, fludarabine 30 mg/m² once daily by IV infusion Days 2 through 6, cytarabine 2000 mg/m² once daily by IV infusion Days 2 through 6, idarubicin 10 mg/m² once daily by IV infusion Days 2 through 4.1

XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy regimen.1

Gilteritinib (XOSPATA) is the ONLY Category 1 recommendation in the NCCN Clinical Practice Guidelines (n=247)1

Releasing as:

Indication

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

Important Safety Information

Contraindications

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

Warning: Differentiation Syndrome

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Warnings and Precautions

Differentiation Syndrome (See BOXED WARNING) 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

Posterior reversible encephalopathy syndrome (PRES) 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

Prolonged QT interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hyponatremia may increase the QT prolongation risk. Correct hypokalemia or hyponatremia prior to and during XOSPATA administration.

Pancreatitis 4% of 319 patients treated with XOSPATA in the clinical trials experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

Adverse Reactions

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These were cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%). 7% discontinued XOSPATA treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/malaise (6%).

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities Shifts to grades 3-4 nonhematologic laboratory abnormalities in XOSPATA treated patients included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

Drug Interactions

Combined P-gp and Strong CYP3A Inducers Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases XOSPATA exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

Strong CYP3A Inhibitors Concomitant use of XOSPATA with a strong CYP3A inhibitor increases XOSPATA exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor Concomitant use of XOSPATA may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless its use is considered essential for the care of the patient.

Specific Populations

Lactation Advise women not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.
XOSPATA® (gilteritinib) tablets for oral use

The following is a brief summary of full Prescribing Information. Please see the package insert for full prescribing information.

**WARNING: DIFFERENTIATION SYNDROME**

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

**INDICATIONS AND USAGE**

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

**DOSEAGE AND ADMINISTRATION**

**Patient Selection**

Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

**Recommended Dosage**

The recommended starting dose of XOSPATA is 120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response. Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

**Dose Modification**

Assess blood counts and blood chemistries, including creatine phosphokinase, after initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Intermittent or reduce XOSPATA dosage in patients who have a QTcF >500 m sec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

**CONTRAINDICATIONS**

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

**WARNINGS AND PRECAUTIONS**

**Differentiation Syndrome**

Of 319 patients treated with XOSPATA in the clinical trials, 1% experienced posterior reversible encephalopathy syndrome (PRES). A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

**Prolonged QT Interval**

XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial, 1% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 m sec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

**PANCREATITIS**

Of 319 patients treated with XOSPATA in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

**Embryo-Fetal Toxicity**

Based on findings in animals and its mechanism of action, XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

**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.

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML treated with gilteritinib 120 mg daily in three clinical trials. The median duration of exposure to XOSPATA was 3.6 months (range 0.1 to 43.4 months).

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These included cardiac arrest (1%) and one case of each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

Of the 319 patients, 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (7%) discontinued XOSPATA treatment permanently due to an adverse reaction.

The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

Overall, for the 319 patients, the most frequent (≥10%) all-grade nonhematological adverse reactions reported in patients were transaminase increased (51%), myalgia/arthritis (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%).

The most frequent ≥5% grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/malaise (6%).

Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased...
Differentiation Syndrome

Dose Modification

Administer XOSPATA tablets orally about the same time each day. If a dose of approved tests for the detection of a FLT3 mutation in AML is available at mutation as detected by an FDA-approved test.

INDICATIONS AND USAGE

REFRACTORY ACUTE MYELOID LEUKEMIA (AML) WITH A FMS-LIKE TYROSINE KINASE 3 (FLT3) MUTATION

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test. Of 319 patients treated with XOSPATA in the clinical trials, 4% experienced greater than 500 msec and 7% of patients had an increase from baseline QTc interval (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during treatment with gilteritinib.

ADVERSE REACTIONS

The most common (>1%) adverse reactions leading to discontinuation were edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (33%), headache (30%), and vomiting (29%). Other clinically significant adverse reactions occurring in ≥1% of patients included: infusion-related reaction (35%), pyrexia (32%), febrile neutropenia (28%), and severe neutropenia (28%).

Additional adverse reactions occurring in ≥2% but less than or equal to 10% of patients treated with XOSPATA in clinical trials included cardiac arrest (1%), differentiation syndrome (1%), and urticaria (2%). Other clinically significant adverse reactions occurring in ≥1% of patients treated with XOSPATA in clinical trials included: neutropenia (27%), anemia (25%), thrombocytopenia (24%), and bleeding events (23%).

Drug-Related Deaths

In the 13-week oral repeated dose toxicity studies in rats and dogs, target organs affected by gilteritinib included: bone and bone marrow, liver, adrenal, and kidney.

Drug-Related Changes

Of the 319 patients in clinical studies of XOSPATA, 43% were age 65 years or older, and 13% were 75 years or older. No overall differences in effectiveness or safety were observed between patients age 65 years or older and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with gilteritinib. Gilteritinib was not mutagenic in a bacterial mutagenesis (Ames) assay and was not clastogenic in a chromosome aberration test assay in Chinese hamster lung cells. Gilteritinib was positive for the induction of micronuclei in mouse bone marrow cells from 65 mg/kg (195 mg/m²) the mid dose tested (approximately 2.6 times the recommended human dose of 120 mg). The effect of XOSPATA on human fertility is unknown. Administration of 10 mg/kg/day gilteritinib in the 4-week study in dogs (12 dogs of dosing) resulted in degeneration and necrosis of germ cells and spermatid giant cell formation in the testis as well as single cell necrosis of the epididymal duct epithelia of the epididymal head.

Animal Toxicology and/or Pharmacology

In the 13-week oral repeated dose toxicity studies in rats and dogs, target organs of toxicity included the eye and kidney.

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062

Revised: 05/2019
222317-GLT

Rx Only
© 2019 Astellas Pharma US, Inc.
XOSPATA® is a registered trademark of Astellas Pharma Inc.

© 2019 Astellas Pharma US, Inc.

astellas
077-0601-PM
Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 68.
Clinical Trial Diversity Efforts Gain Steam

by LARRY HANOVER

The need to diversify patient populations in clinical trials has been recognized for nearly 30 years, but representation of Black and Hispanic Americans continues to lag that of White people. Health disparities highlighted by the COVID-19 pandemic and the racial justice movement that unfolded in 2020 have imbued the issue with a fresh urgency.
Clinical Trials Should Join the Real World

THE DISCREPANCY BETWEEN real-world patients and the populations tested in clinical trials for FDA approvals of new drugs and therapeutic regimens has been an area of long-standing concern in the oncology field. Over the past 5 years, the recognition that therapies introduced into clinical practice frequently may not be evaluated in the patients who would most benefit from them has helped spur an effort to broaden clinical trial eligibility criteria.

Starting in 2016, the American Society of Clinical Oncology (ASCO) and the Friends of Cancer Research have proposed a number of revisions. The first round covered criteria for including patients with HIV infection, brain metastases, organ dysfunction, or prior/concurrent malignancies, and minimum age for pediatric patients. Last year, the FDA changed its clinical trial guidance documents to recognize changes for these groups. In February, the ASCO and Friends groups proposed a new set of recommendations covering washout (or waiting) periods and concomitant medication exclusions, performance status, prior therapies, and laboratory reference ranges.1

These changes should help improve clinical trial enrollment for patients in many populations who have been excluded in the past. However, additional efforts are needed to expand the representation of racial and ethnic minorities. In our cover story in this issue of OncologyLive®, experts discuss the challenges that investigators face in recruiting patients from these communities.

Despite the good intentions of many investigators in academia and industry, only 5% of patients enrolled in clinical trials that led to the FDA approval of novel oncology drugs in 2020 were Black or African American and only 6% were Hispanic.2 These numbers reflect an imbalance that has persisted even after the National Institutes of Health recognized the need for diversity in 1993.

Kenneth C. Anderson, MD, a 2014 Giants of Cancer Care® award winner in the myeloma category, is helping to lead an initiative to enroll more African American individuals in clinical trials testing multiple myeloma therapies. Although African American individuals are far more likely to be diagnosed with multiple myeloma and to die of the disease, members of this community made up only 13% of participants in an analysis of large National Cancer Institute trials.3

The blueprint calls for incorporating specific diversity planning, including a diversity officer for phase 2 and 3 studies, and designing trials that cover disease subtypes and features most commonly observed in African American individuals in clinical trials testing multiple myeloma therapies. Although African American individuals are far more likely to be diagnosed with multiple myeloma and to die of the disease, members of this community made up only 13% of participants in an analysis of large National Cancer Institute trials.3

The ultimate goal is to make clinical trial enrollment more reflective of real-world patient populations. That’s a laudable objective that should enhance oncology care for everyone.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
**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

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>85% ORR&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td><strong>64% ORR&lt;sup&gt;1&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 17.5 months</strong></td>
</tr>
<tr>
<td>(95% CI: 12, NE); median follow-up: 7.4 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>(95% CI: 12, NE); median follow-up: 12.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Responses in intracranial lesions were observed in 10 of 11**
previously treated patients with measurable brain metastases<sup>11</sup>
CNS DoR was ≥6 months in all responders with measurable brain metastases<sup>11</sup>
No patients received radiation therapy to the brain within 2 months prior to study entry<sup>11</sup>

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

<table>
<thead>
<tr>
<th>Systemic therapy naïve&lt;sup&gt;1&lt;/sup&gt; (n=8)</th>
<th>Previously treated&lt;sup&gt;1&lt;/sup&gt; (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100% ORR&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td><strong>79% ORR&lt;sup&gt;1&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>(95% CI: 63, 100)</td>
<td>(95% CI: 54, 94)</td>
</tr>
<tr>
<td>12.5% CR + 88% PR</td>
<td>5.3% CR + 74% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 18.4 months</strong></td>
</tr>
<tr>
<td>(95% CI: NE; NE); median follow-up: 8.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>(95% CI: NE; NE); median follow-up: 17.5 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Advanced or Metastatic RET-Mutant MTC

<table>
<thead>
<tr>
<th>Cabozantinib/vandetanib treatment naive (n=88)</th>
<th>Previously treated with cabozantinib and/or vandetanib&lt;sup&gt;1&lt;/sup&gt; (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>73% ORR&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td><strong>69% ORR&lt;sup&gt;1&lt;/sup&gt;</strong></td>
</tr>
<tr>
<td>(95% CI: 62, 82)</td>
<td>(95% CI: 55, 81)</td>
</tr>
<tr>
<td>11% CR + 61% PR</td>
<td>9% CR + 60% PR</td>
</tr>
<tr>
<td><strong>Median DoR was 22.0 months</strong></td>
<td><strong>Median DoR not yet reached</strong></td>
</tr>
<tr>
<td>(95% CI: NE; NE); median follow-up: 7.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>(95% CI: 19.1, NE); median follow-up: 14.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Find RET. Find results on Retevmo.com.**

*Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.<sup>2</sup> Patients previously treated with platinum-based chemotherapy and with measurable CNS lesions at baseline according to IRC assessment.<sup>1</sup> Patients in this cohort received no prior systemic therapy other than radioactive iodine (RAI).<sup>1</sup> Patients in this cohort received a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI.<sup>1</sup> The efficacy of Retevmo was evaluated in 55 patients with RET-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.<sup>1</sup> Patients with advanced or metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and those without prior systemic therapy were enrolled in separate cohorts.<sup>1</sup> Non-metastatic thyroid cancers (non-MTC) by histology included papillary (n=31), poorly differentiated (n=4), anaplastic (n=2), and Hurthle cell (n=1).<sup>1,12</sup> Other tumors included pancreatic cancer (n=7), colon cancer (n=5), and adrenal gland carcinoma (n=1).<sup>1</sup> Number of patients included in the initial efficacy analysis. Efficacy was based on patients who had at least 6 months of follow-up.<sup>1</sup> Efficacy was evaluated in 105 adult patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. All 105 patients received systemic therapy. 58 of the 105 patients received prior anti-PO-1/PD-L1 therapy, and 50 of the 105 patients received a prior multitargeted inhibitor (MKI).<sup>1</sup> Patients with RET-mutant NSCLC and RET-mutant thyroid cancer (non-MTC) were not enrolled in the trial since RET is not the driver of tumor growth in these cancers.<sup>1,12</sup> BID = twice daily; CI = confidence interval; CNS = central nervous system; CR = complete response; DoR = duration of response; NE = not estimable; ORR = objective response rate; PO = orally; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

**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),<sup>1</sup> advanced or metastatic RET fusion-positive thyroid cancer (non-MTC)<sup>4</sup> (n=38), advanced or metastatic RET-mutant MTC (n=306), and certain other advanced solid tumors with RET alterations (n=26).<sup>4</sup> The study enrolled the following cohorts: systemic therapy-naive patients (n=59)<sup>3</sup> and previously treated (n=105<sup>1,2</sup>) patients who had progressed on platinum-based chemotherapy with metastatic RET fusion-positive NSCLC, systemic therapy-naive (n=8)<sup>4</sup> and previously treated (n=19)<sup>1,2</sup>) patients with advanced or metastatic RET fusion-positive thyroid cancer (non-MTC), and treatment-naive (n=88)<sup>1</sup> and previously treated (n=55)<sup>1,2</sup>) 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.<sup>1,4,5</sup> ORR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v1.1.<sup>1</sup> All results reviewed by an IRC.<sup>1,2</sup>
IMPORTANT SAFETY INFORMATION FOR RETEVMO® (selpercatinib 40 mg, 80 mg capsules) (CONT’D)

Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF 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 bradycardia, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

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

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

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

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on 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 LIBRETO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), 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.

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

Common adverse reactions (all grades) occurring in >15% of patients who received Retevmo in LIBRETO-001, were dry mouth (39%), diarrhea (27%), hypertension (25%), fatigue (25%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (13%).

Laboratory abnormalities (all grades; Grade 3–4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETO-001, were AST increased (51%; 6%), ALT increased (45%; 9%), increased total cholesterol (31%; 0.1%), increased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (2%; 2.2), and decreased glucose (22%; 0.7%).

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

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

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

Concomitant use of Retevmo with 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.

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

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

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

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

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

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

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy are radioactive iodine-refractory (if radioactive iodine is 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. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.4% 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 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 bradycardia/tachycardia, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Adjusting treatment 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 concomitantly administered with strong and moderate CYP3A4 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 of 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 transaminits.

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.

RETEVMO™ (selpercatinib) capsules, for oral use

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 women may result in fetal harm and should only be used if the potential benefit justifies the potential risk to the fetus. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during use of RETEVMO.

Infants and Pediatric Patients
Clinical data are not available for RETEVMO for pediatric patients aged 12 years and older. The safety of RETEVMO has not been established in pediatric patients aged 12 years and younger.

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

RETEVMO can cause serious and sometimes fatal adverse reactions, including:

- Hypersensitivity
- Impaired wound healing
- Embryo-fetal toxicity
- QT interval prolongation

Table 1 summarizes the adverse reactions in LIBRETTO-001.

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

<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><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
</tr>
</tbody>
</table>
Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (≥15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue 1</td>
<td>35</td>
</tr>
<tr>
<td>Edema 4</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 4</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
</tr>
<tr>
<td>Diaphores 2</td>
<td>16</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval 17</td>
<td>4</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage 1</td>
<td>15</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 CYP3A4 Inhibitors
Concomitant use of RETEVMO with a strong or moderate CYP3A4 inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A4 inhibitors with RETEVMO. If concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A4 Inducers
Concomitant use of RETEVMO with a strong or moderate CYP3A4 inducer decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A4 inducers with RETEVMO.

Effects of RETEVMO on Other Drugs
CYP2C8 and CYP3A Substrates
RETEVMO 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
RETEVMO 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 its effects on the breastfeeding 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.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO†</th>
</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>

† 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.
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

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

Males

Advises 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 pharmacokinetic 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 physesal 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 physesal 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 discolouration 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 RETEVMO 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 [CLcr] ≥30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr <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.
From the Editor

Missteps Highlight the Need for Objectivity in Science

by MAURIE MARKMAN, MD

This is an awkward time for the scientific community. Although the spectacular success associated with the development of several safe and highly efficacious vaccines and therapies for COVID-19 has once again confirmed the remarkable impact of advancements on public and individual health, we must also acknowledge recent stunning examples of the failure of scientifically oriented government agencies to provide objectively valid nonpolitical recommendations, policies, and conclusions.

The most recent example is the severely criticized report from a World Health Organization (WHO) investigative team that visited China with the intent of exploring the origin of the virus that causes COVID-19. Access to vital data was blocked by the host country and the report itself had to be approved by the Chinese government. Is it possible that such an inherently flawed effort can be considered scientifically objective?

As stated in a recent editorial in The Wall Street Journal, “The document is best understood as a whitewash heavily influenced by the Chinese Communist Party and Westerners with conflicts of interest.” Those described as having a “conflict of interest” are internationally recognized scientists.

There is no intent in these comments to suggest an alternative conclusion to that reached by the visiting WHO scientists and their Chinese colleagues, but rather to suggest, as noted by experts in this scientific arena, that the process undertaken here may reasonably be viewed more as theater than as a critically essential and objectively valid epidemiologic investigation.

The goal of discussing this shameful, even disastrous excursion by members of the international scientific establishment into geopolitical politics is to highlight the impact of such nonsense on the public’s support, both in the United States and worldwide, for the fundamental integrity of the scientific mission itself.

In addition, the inability of leaders of the scientific community in Europe to agree on a strategy to investigate and subsequently interpret findings involving a small number of thromboembolic events possibly associated with the AstraZeneca’s COVID-19 vaccine also must raise doubt among many members of the public regarding the reliability of official governmental pronouncements about the safety of this and other vaccine products.

Unfortunately, these are not the only serious episodes arising from the COVID-19 pandemic that have challenged the objectivity, validity, and basic quality of the scientific enterprise. The authors of a recently published manuscript highlight “the failure of the scientific enterprise in its initiatives to address the COVID-19 outbreak as a consequence of the disarray attributable to haste and urgency.” The report noted the widespread uploading of research results into publicly viewable preprint internet servers that were reported by the lay media before essential peer review had been initiated, the publication of “underpowered and poorly conducted randomized controlled trials,” and the retraction of several high-profile manuscripts authored by major academic leaders that used a questionable data base (Surgisphere).

None of this can have a positive effect on the public’s perception of and trust in the scientific enterprise. For scientific organizations and public health officials to have credibility, it is essential that society has trust in the data they present, the conclusions they make, and recommendations they provide.

Controversy in Oncology

Although the shortcomings in some COVID-19 reports are glaring, oncology science is not immune from concerns about inadequate objectivity and potentially flagrant bias. Consider a recently published research letter in JAMA Internal Medicine regarding screening mammography recommendations by breast cancer centers in the United States and an accompanying editorial in the journal. Both the research letter and editorial conclude that many breast centers, including some of the leading academic and clinical programs in the country, fail to follow the most recent recommendations of the US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS), and go so far as to suggest in the manuscripts that these decisions may be at least partly financially motivated. In a rebuttal to these manuscripts, the American College of
Radiology (ACR) noted that other highly regarded nationally recognized specialty medical organizations disagreed with the USPSTF/ACS recommendations and provided breast cancer survival data to support their criticism.\(^9\)

Although the ACR unquestionably is an interested party in this debate, the material provided by the society in its rebuttal reveals a lack of full disclosure of the issues in the journal publications and the potential bias exhibited by the authors. Again, such discourse, which is likely to reach the lay media, challenges the objectivity of the peer review literature, editorial commentary, and ultimately the scientific community in the eyes of the public.

Finally, we must acknowledge those experts whose claim to fame may be solely the provision of a dissenting view. Although differing perspectives are not inappropriate, and often quite welcome, the concern arises when such individuals are provided a high-profile scientific publishing forum through which they declare their opinions. For example, an editorialist with an established distain for the concept of precision cancer medicine, using limited published data and his own approach to objective science, proclaimed: “I estimate that precision oncology will benefit around 1.5% of patients with relapsed and refractory solid tumors,” and added, “It is on this tiny proportion of patients that the hopes for precision oncology have been built.”\(^11\)

Although an effective rebuttal to this biased analysis was subsequently published,\(^12\) the point to be made here is a plea to the scientific community to constantly focus on the requirement for objectivity among its members, especially in communications that are relevant to individual and public health.

REFERENCES

The first and only 1L aRCC combination treatment to double PFS and ORR while delivering superior OS

More than 16 months median PFS

PFS benefits observed regardless of IMDC risk group

CheckMate-9ER was 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. 

*PFS and ORR were assessed by BICR.

IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea. Grade 3 diarrhea that cannot be managed with standard anti-diarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% 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 10% of patients. ALT or AST >3 times ULN (Grade ≥3) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab.

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 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 (1.3%) 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 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. 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.
More than double ORR†

55.7% (180/323)
8% CR
48% PR

27.1% (89/328)
4.6% CR
23% PR

CABOMETYX + OPDIVO (n=323)
sunitinib (n=328)

ORR: P<0.0001

5.6% of patients had progressive disease with CABOMETYX + OPDIVO vs 13.7% of patients with sunitinib†

†PFS and ORR were assessed by BICR.

Superior OS outcomes†

40% reduction in risk of death with CABOMETYX + OPDIVO (HR=0.60; 98.89% CI: 0.40-0.89; P=0.0010)
— Median OS not reached in either treatment arm

New CABOMETYX combination starting dose

CABOMETYX 40 mg starting dose—optimized for combination treatment with OPDIVO†

CABOMETYX
40 mg
once daily

OPDIVO
240 mg
every 2 weeks
(30-min IV infusion)
or
480 mg
every 4 weeks
(30-min IV infusion)

IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS

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 development of ONJ until complete resolution.

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

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

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

ADVERSE REACTIONS

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

CABOMETYX as a single agent: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John’s wort.

USE IN SPECIFIC POPULATIONS

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

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

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.

SAFETY: 7

TRIM: 7.875

BLEED: 8.375

A-SIZE PAGE: CA-1749 CABOMETYX NOW APPROVED 9ER 3 PAGE JOURNAL AD / BRIEF SUMMARY / PAGE 1

6. ADVERSE REACTIONS

The safety and efficacy of CABOMETYX were evaluated in a phase 3 randomized, double-blind, placebo-controlled study in patients with advanced renal cell carcinoma (RCC). The study included 334 patients, of whom 168 were treated with CABOMETYX and 166 were treated with placebo. The most common adverse reactions reported in patients treated with CABOMETYX were fatigue, diarrhea, and mucositis.

Diarrhea was the most common adverse reaction, occurring in 40% of patients treated with CABOMETYX compared to 7% of patients treated with placebo. Mucositis was reported in 37% of patients treated with CABOMETYX compared to 8% of patients treated with placebo. Other adverse reactions included fatigue, diarrhea, nausea, and anemia.

Table 1: Adverse Reactions Among the 168 Patients Who Received CABOMETYX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=168)</th>
<th>Placebo (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (%)</td>
<td>63</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Mucositis (%)</td>
<td>44</td>
<td>16</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=168)</th>
<th>Placebo (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (%)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>White Blood Cells (x10^9/L)</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>134</td>
<td>134</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

7. DISCUSSION

In conclusion, CABOMETYX demonstrated a favorable safety profile in the treatment of advanced RCC. The most common adverse reactions were diarrhea, fatigue, and mucositis. Treatment-related adverse reactions were reported in 63% of patients treated with CABOMETYX compared to 10% of patients treated with placebo.

8. REFERENCES


9. CONCLUSION

CABOMETYX was well-tolerated and showed promise in the treatment of advanced RCC. Further studies are needed to confirm these findings and to determine the optimal dose and schedule for this agent.

10. ACKNOWLEDGMENTS

The authors acknowledge the contributions of all study participants and the support of the study staff. This study was funded by Exelixis, Inc.

11. ORCID

[Author's ORCID]

12. COPYRIGHT

© 2020 Exelixis, Inc.

13. ADDITIONAL INFORMATION

For more information, please visit the CABOMETYX website or contact the Exelixis, Inc. Medical Information department.
Table 6: Adverse Reactions occurring in 1% or CABOMETYX Treated Patients in CELEBRATE

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Diathesis</td>
<td>34</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>Urinary Infection</td>
<td>54</td>
<td>15</td>
<td>0.0009</td>
</tr>
<tr>
<td>Hemorrhagic Diathesis</td>
<td>2</td>
<td>1</td>
<td>0.0004</td>
</tr>
<tr>
<td>Urinary Infection</td>
<td>6</td>
<td>2</td>
<td>0.0007</td>
</tr>
<tr>
<td>Hemorrhagic Diathesis</td>
<td>6</td>
<td>2</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Table 7: Laboratory Abnormalities Occurring in 3% or CABOMETYX Treated Patients in CELEBRATE

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>57</td>
<td>5</td>
</tr>
<tr>
<td>Hematologic</td>
<td>57</td>
<td>5</td>
</tr>
<tr>
<td>Hematologic</td>
<td>57</td>
<td>5</td>
</tr>
<tr>
<td>Hematologic</td>
<td>57</td>
<td>5</td>
</tr>
</tbody>
</table>

Factor A: A significant increase in hematopoetic stem cell transplantation is observed in patients treated with CABOMETYX compared to those treated with Placebo. This effect is seen in all hematopoetic stem cell transplantation categories, including myeloablative, non-myeloablative, and autologous.

6. USE IN SPECIFIC POPULATIONS

6.1. Pediatric Use

CABOMETYX is not recommended for use in pediatric patients due to the lack of adequate safety and efficacy data.

6.2. Geriatric Use

CABOMETYX is not recommended for use in elderly patients due to the lack of adequate safety and efficacy data.

6.3. Renal Impairment

In patients with renal impairment, CABOMETYX should be administered with caution and the dose should be adjusted based on the degree of impairment.

7. DRUG INTERACTIONS

7.1. Effects of Other Drugs on CABOMETYX

Concomitant use of CABOMETYX with other antithrombotic agents, such as aspirin, may increase the risk of bleeding.

8. ADVERSE REACTIONS

8.1. Hematologic

CABOMETYX may cause hematopoetic stem cell transplantation, which may delay the onset of sexual maturation. This effect is seen in all hematopoetic stem cell transplantation categories, including myeloablative, non-myeloablative, and autologous.

9. USE IN SPECIFIC POPULATIONS

9.1. Pediatric Use

CABOMETYX is not recommended for use in pediatric patients due to the lack of adequate safety and efficacy data.

9.2. Geriatric Use

CABOMETYX is not recommended for use in elderly patients due to the lack of adequate safety and efficacy data.

9.3. Renal Impairment

In patients with renal impairment, CABOMETYX should be administered with caution and the dose should be adjusted based on the degree of impairment.

10. CONCLUSION

CABOMETYX is a potent and selective inhibitor of VEGF and PDGF receptors, which are involved in the proliferation and survival of endothelial cells. It is being studied in various clinical trial settings as a potential therapeutic agent for a variety of diseases.

11. OVERDOSAGE

No specific antidote is available for CABOMETYX overdose. Supportive care should be provided to manage any associated symptoms.

12. PATIENT COUNSELLING

No patient specific counseling is required for CABOMETYX use. General information regarding the need for a healthy diet, lifestyle modifications, and regular follow-up visits should be provided.

13. pH INTOLERANCE

No information is available on the use of CABOMETYX in patients with pH intolerance.

14. INDICATIONS

CABOMETYX is approved for the treatment of various solid tumors, including renal cell carcinoma, non-small cell lung cancer, and melanoma.

15. PHARMACOKINETICS

CABOMETYX is orally administered and has a half-life of 4.5 days. It is primarily excreted unchanged through the gastrointestinal tract.

16. CLINICAL PHARMACOLOGY

CABOMETYX is a selective inhibitor of VEGF and PDGF receptors, which are involved in the proliferation and survival of endothelial cells.

17. REPORTABLE ADVERSE REACTIONS

No adverse reactions are expected with CABOMETYX use. However, regular follow-up visits and monitoring of vital signs are recommended.

18. PRECAUTIONS

CABOMETYX should be used with caution in patients with a history of bleeding or thrombosis.

19. ADVERSE REACTIONS

CABOMETYX is generally well-tolerated, and the most common adverse events reported include fatigue, nausea, and headache.

20. DOSAGE AND ADMINISTRATION

CABOMETYX is usually administered orally, with a dose of 4 mg/kg body weight once daily. The dose may be adjusted based on individual patient needs.

21. STORAGE

CABOMETYX should be stored at room temperature and protected from light and moisture.

22.erlanding,

A-SIZE PAGE:

CA-1749 CABOMETYX NOW APPROVED 9ER 3 PAGE JOURNAL AD / BRIEF SUMMARY / PAGE 3
Sacituzumab Govitecan Moves Ahead Across Tumor Types

The FDA has granted an accelerated approval to sacituzumab govitecan-hziy (Trodelvy) for the treatment of patients with locally advanced or metastatic urothelial cancer who previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. Additionally, the agency granted regular approval to the agent for patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) who have previously received 2 or more systemic therapies, at least 1 of them for metastatic disease.

The Trop-2–directed antibody-drug conjugate was evaluated for patients with urothelial cancers, in the phase 2 TROPHY U-01 trial (IMMU-132-06; NCT03547973). Results from the trial showed that 112 patients treated with sacituzumab govitecan had a confirmed objective response rate of 27.7% (95% CI, 19.6%-36.9%), which included a 5.4% complete response rate and a 22.3% partial response rate. The median duration of response achieved with sacituzumab govitecan was 7.2 months (95% CI, 4.7-8.6; range, 1.4+ to 13.7).

In patients with TNBC, the FDA reviewed data from the confirmatory phase 3 ASCENT trial (NCT02574455). Among all randomized patients, the median progression-free survival with sacituzumab govitecan was 4.8 months (95% CI, 4.1-5.8) vs 1.7 months (95% CI, 1.5-2.5) with chemotherapy (HR, 0.43; 95% CI, 0.35-0.54; P < .0001). This translated to a 57% reduction in the risk of disease worsening or death. Moreover, the median overall survival was 11.8 months (95% CI, 10.5-13.8) and 6.9 months (95% CI, 5.9-7.6) in the investigative and chemotherapy arms, respectively (HR, 0.51; 95% CI, 0.41-0.62; P < .0001). The approval was based on findings from population pharmacokinetic modeling analyses that compared the predicted exposures of cetuximab delivered at a biweekly dose of 500 mg with observed exposures in patients who received the agent at a weekly dose of 250 mg.

Additionally, the application was supported by data from pooled analyses of overall response rates, progression-free survival, and overall survival from published literature on cetuximab in patients with CRC and SCCHN. Efficacy data from the analyses were consistent across dosage regimens examined and served to further support data reported in the population pharmacokinetic modeling analyses.

The FDA approved the application approximately 5 months ahead of its goal date.

Nivolumab Combo Gains Approval for Gastric Cancers

The FDA has approved the combination regimen of nivolumab (Opdivo) with select types of chemotherapy for the front-line treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer (GEJ), and esophageal adenocarcinoma.

The decision was based on data from the phase 3 CheckMate 649 trial (NCT02872116), which showed that nivolumab in combination with leucovorin, 5-fluorouracil, and oxaliplatin or capecitabine and oxaliplatin resulted in a significant improvement in survival in treatment-naïve patients who had PD-L1–positive advanced gastric cancer, GEJ cancer, and esophageal adenocarcinoma compared with chemotherapy alone.

At a minimum follow-up of 12 months, the median overall survival reported with nivolumab plus chemotherapy was 14.4 months (95% CI, 13.1-16.2) compared with 11.1 months with chemotherapy alone (95% CI, 10.0-12.1) in patients who had a PD-L1 combined positive score of 5 or greater, translating to a 29% reduction in the risk of death with the nivolumab combination (HR, 0.71; 98.4% CI, 0.59-0.86; P < .0001). Moreover, nivolumab plus chemotherapy resulted in a 32% reduction in the risk of disease progression or death compared with chemotherapy alone (HR, 0.68; 95% CI, 0.56-0.81; P < .0001).

New Dosing Regimen for Cetuximab Gets Green Light in CRC and SCCHN

The FDA has approved a new biweekly dosing regimen of 500 mg/m² as a 120-minute intravenous infusion of cetuximab (Erbitux) for patients with KRAS wild-type, EGFR-expressing metastatic colorectal cancer (CRC) or squamous cell carcinoma of the head and neck (SCCHN).

The approval was based on findings from population pharmacokinetic modeling analyses that compared the predicted exposures of cetuximab delivered at a biweekly dose of 500 mg with observed exposures in patients who received the agent at a weekly dose of 250 mg.

Additionally, the application was supported by data from pooled analyses of overall response rates, progression-free survival, and overall survival from published literature on cetuximab in patients with CRC and SCCHN. Efficacy data from the analyses were consistent across dosage regimens examined and served to further support data reported in the population pharmacokinetic modeling analyses.

The FDA approved the application approximately 5 months ahead of its goal date.
Phase 1 Study Launches to Evaluate DNX-2440 for Patients With Liver Metastasis

DNAtrix recently announced the treatment of the first patient enrolled to a phase 1 dose-escalation and dose-expansion study of DNX-2440 (NCT04714983) in patients with resectable liver metastasis. DNX-2440 is a replication-competent, potent, oncolytic adenovirus expressing human OX40 ligand and is expected to enhance antitumor immune responses by providing costimulatory signals to T cells within the tumor microenvironment. As it infects and kills cancer cells, DNX-2440 replicates and triggers both innate and adaptive immune responses.

Investigators will evaluate 24 to 30 patients with resectable multifocal liver metastasis who are scheduled to have liver resection with curative intent. They will have 1 lesion injected with DNX-2440 2 times, 2 weeks apart. The primary end point of the study is to establish safety and identify a maximum-tolerated dose.

“We think that this unique immunotherapy might provide that kind of immune spark, that stimulation, needed to really have an impact in these tumors,” Brett Ewald, PhD, senior vice president of development for DNAtrix, explained in an interview with OncologyLive®. “We’re really just adding on to the standard of care. Patients are already scheduled for surgery to remove these tumors, and if you add a dose or 2 of DNX-2440 before the scheduled surgery and that effects the disease in a positive manner, you can see why that would be very beneficial to patients.”

MT-401 Resumes Evaluation in Posttransplant Setting for Patients With AML

The multitumor-associated antigen (MultiTAA)-specific T-cell product MT-401 is under investigation in a phase 2 trial (NCT04511130) as a potential treatment option for patients with acute myeloid leukemia (AML) following allogeneic stem cell transplant in both the adjutant and active disease settings. The drug was granted an orphan drug designation by the FDA in 2020. The FDA lifted a partial hold on the trial in January 2021 following the resolution of manufacturing questions. The first patient on the trial was dosed with MT-401 in March 2021.

The phase 2 trial will evaluate the safety and efficacy of MT-401. Approximately 120 patients in the adjutant setting will be randomized 1:1 to receive either MT-401 at 90 days following transplant or standard-of-care observation. MT-401 will also be administered to 40 patients with active disease as part of a single arm.

The primary end points of the trial are relapse-free survival for the arm with adjutant disease and complete response and duration of that response for the cohort with active disease. A top-line readout of the active disease group in the trial is anticipated in the first quarter of 2022.

EPI-7386 Plus Enzalutamide Being Evaluated in mCRPC

EPI-7386, a first-in-class N-terminal domain androgen receptor (AR) inhibitor, is being examined in combination with enzalutamide (Xtandi) in patients with metastatic castration-resistant prostate cancer (mCRPC) as part of a phase 1/2 trial. In September 2020, the FDA granted fast track designation to EPI-7386 for the treatment of adult patients with mCRPC who are resistant to standard-of-care options.

The new study is the product of a clinical collaboration forged between ESSA Pharma Inc, the manufacturer of EPI-7386, and Astellas Pharma Inc. Per the terms of their supply agreement, ESSA Pharma Inc will sponsor the trial and retain all rights to EPI-7386, while Astellas Pharma Inc will supply enzalutamide for the research.

The trial will evaluate the combination in patients with mCRPC who have not received prior treatment with second-generation androgen therapies and is slated to begin enrollment in 2021. Results from an AR-driven cellular model showed that EPI-7386 inhibits the androgen-regulated transcriptome similarly to enzalutamide but with a few notable qualitative and quantitative differences. Further, investigators reported that the combination treatment of EPI-7386 with enzalutamide displayed “broader and deeper inhibition of AR-associated transcriptional activity than higher doses of each single agent alone.”

Companion Diagnostic for Immunotherapy Is Under Development in HPV-Associated Cervical Dysplasia

QIAGEN and INOVIO Pharmaceuticals, Inc, have reached an agreement to develop liquid biopsy-based companion diagnostic assays for INOVIO agents. The collaboration’s goal is to utilize QIAGEN’s bioinformatic expertise to further the predictive power of the preliminary biomarker signature developed by INOVIO. Under the partnership, the companies will focus on codeveloping a companion diagnostic test that can inform clinicians as to which patients with advanced human papillomavirus (HPV)-associated cervical dysplasia are likely to benefit from VGX-3100, a DNA-based medicine that utilizes the patient’s immune system to clear HPV-16/18-associated high-grade precancerous lesions. VGX-3100 is being developed for use in anal, vulvar, and cervical dysplasia. The agent is under evaluation in 2 phase 3 clinical trials, REVEAL 1 (NCT03185013) and REVEAL 2 (NCT03721978).

The assay will be developed for use on the Illumina NextSeq 5500x instrument, which allows for next-generation sequencing in vitro diagnostic testing.
Thank you for your nominations for the 2021 Class of Giants of Cancer Care®

The newest class of Giants will be announced in mid-September of 2021 and will be honored at an awards ceremony on November 4, 2021.

For more information visit giantsofcancercare.com
**Tivozanib Boosts RCC Treatment Portfolio**

**by KYLE DOHERTY**

**THE FDA’S APPROVAL OF TIVOZANIB** (Fotivda) adds an effective treatment option with a manageable safety profile for patients with relapsed or refractory renal cell carcinoma (RCC), according to Daniel J. George, MD.1

In vitro cellular kinase assays showed that the tyrosine kinase inhibitor (TKI) inhibits the phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3.2 The agent was evaluated in the phase 3 TIVO-3 trial (NCT02627963), which compared tivozanib with sorafenib (Nexavar) in patients with refractory advanced RCC.

Efficacy data from the trial showed that the median progression-free survival (PFS) in the tivozanib group (n = 175) was 5.6 months (95% CI, 4.8-7.3) compared with 3.9 months (95% CI, 3.7-5.6) in the sorafenib group (n = 175). The objective response rate was 18% (95% CI, 12%-24%) in the tivozanib arm vs 8% (95% CI, 4%-13%) in the sorafenib arm.

In an interview with OncologyLive®, George, director of genitourinary oncology at Duke University Cancer Institute (DCI), and cochair of DCI Center for Prostate & Urologic Cancers in Durham, North Carolina, discussed how tivozanib differs from other TKIs and its potential to fill an unmet need in the treatment of patients with RCC.

**Please provide an overview of the patient population in the TIVO-3 trial.**

TIVO-3 examined a population of patients with refractory kidney cancer. These are patients with metastatic kidney cancer, clear cell type, who have already previously been treated with a TKI and an immunotherapy and were in either the third- or fourth-line setting of treatment. Patients could have had more than 1 of either of those regimens. Patients were randomized 1:1 to either sorafenib, an FDA-approved VEGF TKI used frequently in the refractory disease setting, or tivozanib, which had been approved in Europe based on a frontline study against sorafenib.

**What was noteworthy about the efficacy data that led to the approval?**

There were 2 noteworthy components to this trial. The first was that for the intention-to-treat population we saw a statistically significant improvement in the PFS associated with tivozanib vs sorafenib, which was approximately a 30% improvement in HR, delaying the time to disease progression. The second is that, in a prespecified subset analysis looking at patients who were immediately proceeded by an I/O [immuno-oncology] therapy, there was an even greater PFS benefit seen with the subsequent use of tivozanib vs sorafenib. This suggests that this agent may be particularly useful in patients who are refractory to I/O agents, and it also suggests that this agent could work well in combination with I/O agents, which we’re seeing now as a standard of care in the frontline setting.

The last thing that’s interesting from both the Kaplan-Meier curves from this study is the tail of the curve. There are approximately 20% to 30% of patients who have a much more durable PFS associated with tivozanib than sorafenib. It seems as though there’s a subset of patients who appear to have VEGF-dependent RCC, even in this refractory state. Tivozanib was a drug that most patients were able to tolerate at or near full dosage; that’s important in a refractory patient population. Many of these patients are refractory in part due to difficulty tolerating these agents and are at a point in their disease where they’re dealing with the symptoms of the disease as well as prior therapies. Tolerance becomes a critical and often differentiating factor in their survival.

**Regarding safety, what do we know about tivozanib’s tolerability, and what adverse events should be taken into consideration when it is administered?**

Even though we have several VEGF TKIs in the field, tivozanib has the greatest potency. It’s dosed at the lowest level of any VEGF TKI and it’s highly specific for the VEGF receptors. [Tivozanib] also has a relatively long half-life. There are biologic and toxicity ramifications of these features. Due to the VEGF specificity and high potency, we see an adverse effect profile that’s a little more narrowed around VEGF toxicities, including hypertension, diarrhea, fatigue, and dysphonia, in this refractory population. We’re also recognizing that blood pressure might need to be adjusted in this patient population.

It’s important to recognize that this toxicity is manageable. We’re able to dose this drug daily with a relatively long half-life. That’s important regarding toxicities that might be a bit more episodic, things such as nausea and diarrhea.

**How does this approval advance the RCC treatment paradigm?**

There’s a lot of progress being made in RCC in the frontline space with combinations of I/O therapy or I/O and TKI therapy. This suggests that for those patients who can tolerate those regimens, there’s a lot of benefit. However, most of those patients are still going to progress. When they progress, now having been exposed to multiple classes of drugs, it’s critical that there is tolerable therapy. What we’ve learned over the past 15 years in RCC is that the sequence of one TKI after another has been associated with a longer survival than switching to other classes or no therapy at all. Tivozanib fills an unmet need in the RCC space for patients who struggle to tolerate multitargeted VEGF TKIs that may be causing additional toxicity. It allows patients to potentially remain on treatment and to significantly delay the time to disease progression.

**What are the next steps for tivozanib?**

It’s important to understand the unique features of this drug, to help educate clinicians about its differentiating characteristics, and [to encourage them] to use it in their patients in this disease setting. Also, it’s important that the [investigators] begins to revisit some earlier disease settings that TKIs are being used in because we see a significant number of toxicities with those combinations and much of that is driven by the TKI of choice. Tivozanib needs to be able to generate data that show that it is active in that combination setting. It is also tolerable in combination with I/O therapy, which will be an important future direction. ■

**REFERENCES**


**Mechanism of action:**
- Tivozanib inhibits phosphorylation of VEGFR-1, VEGFR-2, and VEGFR-3 and inhibits other kinases including c-KIT and PDGFR β at clinically relevant concentrations. Tivozanib also inhibits angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human RCC.

**How supplied:**
- 1.34- and 0.89-mg capsules

**Dosing:**
- 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment in 28-day cycles until disease progression or unacceptable toxicity

**Company:** AVEO Pharmaceuticals, Inc

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Tivozanib (n = 175)</th>
<th>Sorafenib (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 (34-88)</td>
<td>63 (30-90)</td>
<td></td>
</tr>
</tbody>
</table>

**IMDC risk category (%)**

<table>
<thead>
<tr>
<th>Tivozanib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>69% Favorable</td>
<td>61% Favorable</td>
</tr>
<tr>
<td>15% Intermediate</td>
<td>20% Intermediate</td>
</tr>
<tr>
<td>17% Poor</td>
<td>19% Poor</td>
</tr>
</tbody>
</table>

**Prior therapies (%)**

<table>
<thead>
<tr>
<th>Tivozanib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>46% 2 VEGFR TKIs</td>
<td>49% 2 VEGFR TKIs</td>
</tr>
<tr>
<td>27% Checkpoint inhibitor plus VEGFR TKI</td>
<td>26% Checkpoint inhibitor plus VEGFR TKI</td>
</tr>
<tr>
<td>27% VEGFR TKI plus other systemic agent</td>
<td>26% VEGFR TKI plus other systemic agent</td>
</tr>
</tbody>
</table>

**Number of metastatic sites (%)**

<table>
<thead>
<tr>
<th>Tivozanib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 1</td>
<td>60 2</td>
</tr>
<tr>
<td>30 2</td>
<td>26 2</td>
</tr>
<tr>
<td>7 3</td>
<td>14 3</td>
</tr>
</tbody>
</table>

**Efficacy Results in the Tivozanib (NCT02627963) was a phase 3, randomized, open-label, multicenter trial of tivozanib vs sorafenib in 350 patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments, including at least 1 VEGFR kinase inhibitor other than sorafenib or tivozanib. Patients were randomized to either tivozanib 1.34 mg orally once daily for 21 consecutive days every 28 days or sorafenib 400 mg orally twice a day continuously, until disease progression or unacceptable toxicity.**

**Commonly Reported Adverse Effects in Tivozanib (NCT02627963)**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Tivozanib (n = 173)</th>
<th>Sorafenib (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67% 13%</td>
<td>48% 12%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44% 24%</td>
<td>31% 17%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>17% 3%</td>
<td>12% 1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43% 2%</td>
<td>54% 11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30% 0%</td>
<td>18% 4%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39% 5%</td>
<td>30% 4%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>27% 1%</td>
<td>9% 0%</td>
</tr>
<tr>
<td>Cough</td>
<td>22% 0%</td>
<td>15% 1%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>24% 1%</td>
<td>11% 0%</td>
</tr>
<tr>
<td>Back pain</td>
<td>19% 2%</td>
<td>16% 2%</td>
</tr>
</tbody>
</table>

**Warnings and Precautions**

- Hypertension and hypertensive crisis
- Cardiac failure
- Cardiac ischemia and arterial thromboembolic events
- Venous thromboembolic events
- Hemorrhagic events
- Proteinuria
- Thyroid dysfunction
- Risk of impaired wound healing
- Reversible posterior leuкоencephalopathy syndrome
- Embryo-fetal toxicity
- Allergic reactions to tartrazine

**References**
Drug Spotlight

Trilaciclib Tackles Myelosuppression in SCLC

by KYLE DOHERTY

TRILACICLIB (COSELA) HAS EMERGED as a new supportive treatment option for reducing the frequency of myelosuppression in patients with adults with extensive-stage small cell lung cancer (ES-SCLC) receiving certain types of chemotherapy.

The FDA approved the CDK4/6 inhibitor on February 12, 2021, based on results of 3 phase 2 studies: G1T28-05 (NCT03041311), G1T28-02 (NCT02499770), and G1T28-03 (NCT02514447).

In G1T28-05, investigators examined 107 patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. Patients were randomized to receive either trilaciclib or placebo prior to treatment with etoposide, carboplatin, and atezolizumab (Tecentriq). Results from the trial showed that of 54 patients treated with trilaciclib, 1.9% had severe neutropenia compared with 49.1% of patients in the placebo arm (n = 53).

G1T28-02 was a randomized, double-blind examination of trilaciclib vs placebo administered to participants prior to treatment with etoposide and carboplatin. The trial included 77 patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. Data showed that 5.1% of patients in the trilaciclib arm (n = 39) had severe neutropenia vs 42.1% of patients treated with placebo (n = 38).

In the randomized, double-blind G1T28-03 trial, investigators evaluated trilaciclib vs placebo administered prior to treatment with topotecan in 61 patients with ES-SCLC who were previously treated with chemotherapy. Results showed that 40.6% of patients in the trilaciclib arm (n = 32) had severe neutropenia compared with 75.9% of patients in the placebo group (n = 29).

In an interview with OncologyLive®, Lowell L. Hart, MD, scientific director of clinical research at Florida Cancer Specialists & Research Institute in Fort Myers, discussed trilaciclib’s unique role in patients with ES-SCLC who experience myelosuppression, as well as the future role of the agent.

What was noteworthy about the efficacy data that led to the approval of trilaciclib?

Standard treatment for ES-SCLC for a long time has been to use a platinum agent with an etoposide. More recently, atezolizumab or other immune checkpoint inhibitors have been used. The main issue [we’ve seen] with tolerability when using these agents is that they are all myelosuppressive and cause anemia, thrombocytopenia, and neutropenia. Trilaciclib is a CDK4/6 inhibitor, [known for treating patients with] breast cancer. The idea came about that perhaps a similar drug [that causes] an adverse effect in patients with breast cancer may be a good thing in patients who are receiving myelosuppressant chemotherapy. [Essentially, the agent would be] putting a patients’ bone marrow ‘to sleep’ transiently using a new intravenous formulation. It’s not a drug that you take for 2 weeks straight, but one [that is administered] before the start of chemotherapy, or in the cell cycle right before the chemotherapy hits. [This way we are] protecting the patient from the adverse effects of chemotherapy, which are greater on cells that are dividing vs cells that are “asleep.”

Patients with ES-SCLC have uniformly lost the retinoblastoma protein [RB], so you would not expect that a CDK inhibitor like trilaciclib would have any effect on the cancer. Rather, the agent [is meant to have an effect] on the quality of life of the patients. It’s essentially a supportive care drug, which may be a little hard for some oncologists to wrap their minds around because they’re used to these CDK drugs given with hormone therapy in breast cancer.

[Trilaciclib] did hit its study end points: the duration of severe neutropenia was greatly reduced, quality of life of patients was improved, and the need for RBC [red blood cell] transfusions was [reduced].

How does trilaciclib achieve these outcomes?

Trilaciclib works on the hematopoietic stem cells in the bone marrow by reducing their rate of proliferation, basically trying to [cause this effect] in the G0 phase and out of cell cycle. These cells are very vulnerable to the effects of chemotherapy. We want the chemotherapy to kill off the fast-growing cancer cells and we know, because these patients don’t have RB, they are not going to be affected by this at all. We want the chemotherapy not to affect the bone marrow cells that are equally rapidly turning over, especially neutrophils. By throwing these precursors out of cell cycle, they won’t be adversely affected by chemotherapy.

How does this approval advance the ES-SCLC treatment paradigm?

It’s very helpful. Again, the drug is not going to take a patient who is potentially incurable and make them curable. There’s a lot more focus lately on the patient’s quality of life. If we can preserve these patients’ quality of life—it will eventually deteriorate as their disease progresses—we’re really doing something beneficial for the patient. I believe it’s important for oncologists to not only focus on [whether] the cancer is 20% bigger or 20% smaller, but also on how the patient is doing, if their quality of life is being maintained. Are they not ending up having to sit around their house for 3, 4, or 5 days because they have severe neutropenia? With the use of trilaciclib, oncologists will be more comfortable using a standard dose of topotecan rather than the ad-hoc changes in doses that many of us have done [because of myelosuppressive effects].

What are the next steps for trilaciclib?

The drug’s efficacy in limited-stage disease is an area of interest. It also has had some interesting data in patients with triple-negative breast cancer [TNBC]. This is another disease where you must use chemotherapy and, similar to ES-SCLC, many of these patients have lost RB function. I participated in a study using chemotherapy with and without trilaciclib in TNBC; we saw in the data that it seemed to show some extra effects, perhaps even a little survival benefit. There are some effects that are not totally worked out to the final state yet concerning [how] this drug may [affect] the immune microenvironment. I’m looking forward to continuing to work with the drug in various other settings, seeing what effect it may have on the immune microenvironment, and seeing what other effects it has besides myelopreservation. I think the potential for other uses is out there.

REFERENCES

Drug Spotlight

PIVOTAL CLINICAL TRIAL DESIGN
G1T28-05 (NCT03041311): trilaciclib administered prior to treatment with etoposide, carboplatin, and atezolizumab in patients with newly diagnosed ES-SCLC not previously treated with chemotherapy
G1T28-02 (NCT02499770): trilaciclib administered prior to treatment with etoposide and carboplatin in patients with newly diagnosed ES-SCLC not previously treated with chemotherapy
G1T28-03 (NCT02514447): trilaciclib administered prior to topotecan in patients with ES-SCLC previously treated with chemotherapy

BASELINE PATIENT CHARACTERISTICS
(from pooled analysis of G1T28-02, G1T28-05, and G1T28-03)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo prior to chemotherapy (n = 119)</th>
<th>Trilaciclib prior to chemotherapy (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>64 (39-88)</td>
<td>64 (45-82)</td>
</tr>
<tr>
<td>Placebo prior to chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LDH (%)</td>
<td>51.3 ≤ ULN</td>
<td>45.4 &gt; ULN</td>
</tr>
<tr>
<td>ECOG performance status (%)</td>
<td>0-1 89.9</td>
<td>0-1 87.8</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>0-1 89.9</td>
<td>0-1 87.8</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase; ULN, upper limit of normal.

REFERENCES

Efficacy Results in G1T28-05

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trilaciclib (n = 54)</th>
<th>Placebo (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSN in cycle 1, days</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Patients with severe neutropenia</td>
<td>1.9%</td>
<td>49.1%</td>
</tr>
<tr>
<td>All-cause dose reductions, event rate/cycle</td>
<td>0.021</td>
<td>0.085</td>
</tr>
<tr>
<td>Patients with RBC transfusion at/after 5 weeks</td>
<td>13.0%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Patients with G-CSF administration</td>
<td>29.6%</td>
<td>47.2%</td>
</tr>
</tbody>
</table>

Efficacy Results in G1T28-02

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trilaciclib (n = 39)</th>
<th>Placebo (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSN in cycle 1, days</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Patients with severe neutropenia</td>
<td>5.1%</td>
<td>42.1%</td>
</tr>
<tr>
<td>All-cause dose reductions, event rate/cycle</td>
<td>0.022</td>
<td>0.084</td>
</tr>
<tr>
<td>Patients with RBC transfusion at/after 5 weeks</td>
<td>5.1%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Patients with G-CSF administration</td>
<td>10.3%</td>
<td>63.2%</td>
</tr>
</tbody>
</table>

Efficacy Results in G1T28-03

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trilaciclib (n = 32)</th>
<th>Placebo (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSN in cycle 1, days</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Patients with severe neutropenia</td>
<td>40.6%</td>
<td>75.9%</td>
</tr>
<tr>
<td>All-cause dose reductions, event rate/cycle</td>
<td>0.051</td>
<td>0.116</td>
</tr>
<tr>
<td>Patients with RBC transfusion at/after 5 weeks</td>
<td>31.3%</td>
<td>41.4%</td>
</tr>
<tr>
<td>Patients with G-CSF administration</td>
<td>50.0%</td>
<td>65.5%</td>
</tr>
<tr>
<td>Patients with platelet transfusion</td>
<td>25.0%</td>
<td>31.0%</td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS
- Injection-site reactions, including phlebitis and thrombophlebitis
- Acute drug hypersensitivity reactions
- Interstitial lung disease/pneumonitis
- Embryo-fetal toxicity

Company: G1 Therapeutics, Inc

Trilaciclib (Cosela) FDA approval—February 12, 2021
FDA grants approval for the kinase inhibitor to reduce the frequency of chemotherapy-induced myelosuppression in adults receiving a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

Mechanism of action:
- Trilaciclib transiently inhibits CDK4 and CDK6.
- Hematopoietic stem and progenitor cell proliferation in the bone marrow is dependent on the CDK4/6 pathway and gives rise to circulating neutrophils, red blood cells, and platelets.

How supplied:
- 300 mg as a yellow lyophilized cake in a single-dose vial

Dose:
- The recommended dose is 240 mg/m² as a 30-minute intravenous infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

Company: G1 Therapeutics, Inc
FOR ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

BRUKINSA STAYS ON, SO

BRUKINSA STAYS OFF

24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.¹²

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemotorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman.
BRUKINSA—THE BTK INHIBITOR DEMONSTRATED TO PROVIDE COMPLETE AND SUSTAINED INHIBITION1,2

POWERFUL RESPONSES1

<table>
<thead>
<tr>
<th>STUDY 206</th>
<th>PET-BASED1</th>
</tr>
</thead>
<tbody>
<tr>
<td>84% ORR</td>
<td>(95% CI: 74, 91)</td>
</tr>
<tr>
<td>59% CR</td>
<td>(95% CI: 44, 73)</td>
</tr>
<tr>
<td>19.5 mo MEDIAN DOR</td>
<td>(95% CI: 16.6, NE)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY 003</th>
<th>CT-BASED1</th>
</tr>
</thead>
<tbody>
<tr>
<td>84% ORR</td>
<td>(95% CI: 67, 95)</td>
</tr>
<tr>
<td>22% CR</td>
<td>(95% CI: 16, 30)</td>
</tr>
<tr>
<td>18.5 mo MEDIAN DOR</td>
<td>(95% CI: 12.6, NE)</td>
</tr>
</tbody>
</table>

Median follow-up time was 18.4 months for Study 206 and 18.8 months for Study 003.

DEMONSTRATED SAFETY PROFILE1

The most common adverse reactions (≥ 20%) included neutrophil count decreased, platelet count decreased, upper respiratory tract infection, white blood cell count decreased, hemoglobin decreased, rash, bruising, diarrhea, and cough.

The efficacy of BRUKINSA was IRC-assessed in 2 clinical trials that included a total of 118 adult patients with MCL who received at least 1 prior therapy. Tumor response was according to the 2014 Lugano classification for both studies, and the primary efficacy endpoint was ORR as assessed by an IRC. Study BGB-3111-206 (Study 206): N=86, Phase 2, open-label, multicenter, single-arm trial; PET scans were required for response assessment. Study BGB-3111-AU-003 (Study 003): N=32, Phase 1/2, open-label, global, multicenter, single-arm trial; PET scans were not required for response assessment and the majority of patients were assessed by CT scan.

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. 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.

Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions in >10% of patients who received BRUKINSA were decreased neutrophil count (35%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (26%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (13%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. 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.


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

LEARN MORE AT BRUKINSA.com
COVID-19 Has Diverse Effects on Cancer Care

by Kyle Doherty

THE COVID-19 PANDEMIC HAS changed strategies and practices in industries across the world, and oncology is no exception. Almost immediately after the pandemic took hold in the United States in March 2020, oncologists and patients were forced to make changes that were once thought to be impossible or at the very least impractical. The types of adaptations, and their degree, have varied depending on a host of factors, including location, economic standing, and disease status, but almost no practice has gone through the pandemic unaffected.

OncologyLive® Advisory Board members spoke about how COVID-19 has touched all aspects of oncology practice, research, and treatment.

BREAST CANCER

Adam M. Brufsky, MD, PhD
University of Pittsburgh Medical Center

Initially when [the pandemic] became serious, we took a very cautious approach. We tried to postpone surgery and give people neoadjuvant hormonal therapy as much as we could. After the first 6 to 10 weeks, we tried to slowly transition back to a kind of normal practice. For the past year, patients have been very concerned; we tried to validate their concerns and help [treat] their breast cancer. The most important thing about breast cancer is that you shouldn’t put off [methods of] detecting it; you should try to as best you can to do your normal screenings. If you have it, you shouldn’t put off treating it.

There was concern that people who would have ordinarily been treated for their breast cancer decided to postpone because of concerns with COVID-19. This is not ideal because there is a survival benefit to a lot of the treatments we utilize in breast cancer if we use them early—CDK4/6 inhibitors are a perfect example. If we give them earlier in the disease course, there are potential survival benefits. We try to make it as easy as we can with televisits, so the patients continue with their therapy. In terms of volume, we’re back to our prepandemic levels, and we’ve probably been back to that for at least 6 months.

LUNG CANCER

Edward B. Garon, MD
Ronald Reagan UCLA Medical Center

The most visible impact is the increase in video visits. In addition, in some situations, starting cytotoxic chemotherapy was something that I slightly favored in normal times, but slightly disfavored [during the pandemic] because of enhanced concerns about increased risk of infection.

GENITOURINARY

Daniel J. George, MD
Duke University Cancer Center

In March 2020, our clinic largely shut down and we were only seeing the essential active-treatment patients. Our volume decreased dramatically and many patients decided to stop their therapy for a period of time because of the unknowns about COVID-19. Over the course of the past year, we’ve seen that fear wax and wane. There have been a lot of inconsistencies with how we as a staff have reacted to COVID-19. Something that has persisted throughout the whole period is the recognition that cancer care goes on, but it’s been affected by the isolation.

As providers, we continue to work much more siloed than we were [prior to the pandemic]. It’s improved since the first couple of months, but most of our interactions are still [conducted using] Zoom. Even though almost all of our health care providers and support staff are vaccinated, we still have limited in-person meetings, which is not ideal. Much care and research happens in those impromptu, face-to-face interactions that happen when you’re at a critical mass in a health system or in a research institute. It’s definitely affected our culture, beyond these restrictions.

Even now that we’ve been vaccinated and patients have also largely been vaccinated, we’re not back to the way we were. Most of our patients are older than 65 years and I would say 75% to 80% of my patients has been fully vaccinated. Yet, I rarely shake hands with patients and almost never hug a patient. Patients are still reluctant to come in; they’re still reluctant to do therapy because of these inherent risks. That habit has formed now and it’s going to take active energy to change people back to trusting everything from public transportation to restrooms.

Even though we’ve been told that with vaccination we’re safe from this virus, 95% protected, people are still acting as if they’re not safe. That doubt is almost unconscious in their behavior. It’s a concern because it affects their willingness to do all the other things that patients used to take for granted such as participating in clinical trials, going to support-group meetings, or participating in advocacy and fundraising events. I worry that’s not going to change overnight; it’s going to take some real effort, energy, and conviction to [reinforce the message that] those interactions are important in the experience of cancer care.
In the Midwest, COVID-19 arrived late, and we learned a lot from the coastal states. Our clinical trial program never shut down and our oncologic surgeries never shut down. The biggest impact may have been when our patients [received a] diagnosis [of cancer], and the stage at which they showed up. We’re seeing larger tumors and more metastatic extent of disease than we used to see. It’s become more of a treatment challenge for the people who weren’t part of medical care in that year—if you couldn’t get diagnosed, you couldn’t get to us [for treatment].

I think this is probably the biggest impact we’ve seen on care in the Midwest: “I wish I’d seen you earlier.” I’m sure this is happening in other places; people are not getting colonoscopies and that has an affect downstream. Their smaller masses are now larger, so we’ve been a bit more heroic with chemotherapy than we used to be, and we’ve rescued some people.

COVID-19 restricted access by taking away capacity of the in-patient unit, which became dominated by patients with COVID-19. The other impact was on patient confidence to travel [to the facility] and be seen [in person]. We compensated by switching many aspects to telemedicine. The experience, while forced upon us under bad circumstances, has been a good one because we learned by being forced into a new situation. It turns out that much of the business, although certainly not all, can be done remotely. We can talk to patients remotely about their scan and lab results. We don't want to see a new patient remotely; however, it may be a better solution for second opinions for someone who lives farther away.

Prior to the pandemic, [video visits] were something that we were talking about being able to do. When the pandemic [necessitated restrictions], nearly 70% [of our visits became] video visits. We’re closer now to probably 50%, and our goal is to have somewhere in the 30%-to-50% range be video. We’re testing patients monthly for COVID-19 if they’re getting infusions or scans. The providers are all getting tested weekly now. Universal masking was implemented early [and has been] maintained, and I don’t know if that will ever go back to the way it was. We didn’t really change treatments for most of our patients; however, some modifications were made with medications. For example, some infusion therapies that were [being given] every 2 to 3 weeks were shifted to [being given] every 4 to 6 weeks. It’s easier if the patient doesn’t come in very often, and it’s safer for the patient to not have to leave home. However, we don’t get to see the patient as often, either via video or in person. We will continue to decide on an individual basis if a patient is a good candidate for the less frequent visits and less frequent infusions.

It has been a humbling experience, and many of my colleagues would agree with me that this was unexpected. But it also showed how resilient the health care system is in terms of being able to adapt. We were quick to try to find solutions during the crisis. For our patients with head and neck cancer, we relied on a team effort to channel these patients to treatment options that they may not have otherwise considered. We created ad-hoc meetings between different specialists to see if we could treat patients with different modalities if the operation schedule did not permit surgery. We were able to maintain ongoing patient care and facilitate treatment for many of our patients, although the treatment modality may have changed.

Telehealth has been helpful in many instances; however, I don’t believe every patient is ideal for this situation. We’ve seen some patients who were easily followed through telehealth. Some patients who are stable in general were able to do OK with telehealth visits, even though they were on some form of maintenance therapy or had scheduled follow-up visits following definitive therapy. The patients who didn’t continue to do [as well] were patients who may have some technical challenges with calling in on telehealth, patients who cannot really vocalize. For patients in the most need, telehealth has not been proven to be an effective tool. As a result, we’ve seen in the clinic an increase in patients with more acute problems, [beginning] when COVID-19 [cases eased]. We saw a surge in patients with large tumors, patients who have not had adequate investigation and who have not had adequate care. It has been a learning curve, and we’ve learned a lot.

We are utilizing telehealth more (about 15% of patients), which has increased accessibility as well as the speed with which we can resolve patient concerns. What I have noticed the most, though, is a willingness to say, “why not” to many ideas that previously were thought to be unacceptable such as electronic signatures, virtual consenting for studies, administering certain injections at home where previously a visit to the infusion center was required, and virtual consults for focused medical questions.

There has been a stage migration to later stages as many patients are fearful of coming to the hospital. COVID-19 also sped the development of virtual care; however, it is not optimal for all patient situations and [is not likely to become] a permanent part of care. It is very helpful for patients who live farther away, have good [internet] bandwidth, and for whom a physical examination is less helpful. [Virtual consultations are] also good for second opinions as well as for patients who receive targeted therapy.
INDICATION
NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

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

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

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

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

Drug Interactions
Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA

When treating non-metastatic castration-resistant prostate cancer (nmCRPC), METASTASIS-FREE SURVIVAL IS JUST THE HALF OF IT
NUBEQA®—Focus on both MFS and tolerability¹,²

More than double the median MFS with NUBEQA + ADT* vs 18 months with ADT alone¹

(\text{HR}: 0.41; 95\% \text{CI}: 0.34-0.50; \text{P} < 0.0001) *95\% \text{CI}: 34.3-\text{NR}. 95\% \text{CI}: 15.5-22.3.

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%)⁴

9% of men permanently discontinued due to adverse reactions whether on NUBEQA + ADT or ADT alone

Dose interruptions and reductions due to adverse reactions occurred in 13% and 6%, respectively, of patients treated with NUBEQA + ADT.¹

The most frequent reasons for permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%). The most frequent reasons for dose interruptions included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%). The most frequent reasons for dose reductions included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).¹

NUBEQA®—proven to extend MFS, now with statistically significant OS¹,³

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone³

Metastasis-free survival (MFS) was the primary endpoint. Overall survival (OS) was a key secondary endpoint. OS data were not mature at time of first analysis (57% of the required number of events). At final analysis, OS was statistically significant but median not reached. HR: 0.69 (95% CI: 0.53-0.88); P = 0.003.¹,³

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BCRP-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, ¹⁵³⁰C bone scan by BCRP, unacceptable toxicity, or withdrawal.¹,²

¹All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased aspartate aminotransferase (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

NUBEQA®—proved to extend MFS, now with statistically significant OS¹,³

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone³

Metastasis-free survival (MFS) was the primary endpoint. Overall survival (OS) was a key secondary endpoint. OS data were not mature at time of first analysis (57% of the required number of events). At final analysis, OS was statistically significant but median not reached. HR: 0.69 (95% CI: 0.53-0.88); P = 0.003.¹,³

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BCRP-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, ¹⁵³⁰C bone scan by BCRP, unacceptable toxicity, or withdrawal.¹,²

¹All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased aspartate aminotransferase (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

Start new patients with up to 2 months free.*

Visit NUBEQAhcp.com

with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

Effects of NUBEQA on Other Drugs – NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

*The NUBEQA Free Trial Program provides 2 months’ supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions, please call DUDE Access Services at 1-833-337-DUDE (1-833-337-3833) or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions.

ADT=androgen deprivation therapy; BCRP=blinded independent central review; CI=confidence interval; CT=computed tomography; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; MRI=magnetic resonance imaging; NR=not reached.

Please see the following pages for brief summary of full Prescribing Information.
**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

5.1 Embryo-Fetal Toxicity

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

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

**ADVERSE REACTIONS**

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

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

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

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

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

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

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

**Table 1: Adverse Reactions in ARAMIS**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥ 3 %</td>
</tr>
<tr>
<td>Fatigue¹</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>Rash</td>
<td>3.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

¹ Includes fatigue and asthenia

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

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

**Table 2: Laboratory Test Abnormalities in ARAMIS**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4²</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0.7</td>
</tr>
</tbody>
</table>

² The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

**DRUG INTERACTIONS**

7.1 Effect of Other Drugs on NUBEQA

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

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

**CONTRAINDICATIONS**

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

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

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

**USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

**Risk Summary**

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

Animal embryo-fetal development toxicity studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

**Risk Summary**

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

8.3 Females and Males of Reproductive Potential

**Contraception**

Males

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

Fertility

Males

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

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

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

17 PATIENT COUNSELING INFORMATION
Dosage and Administration
Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.
Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.
Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity
Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].
Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

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

Clinical Trial Diversity Efforts Gain Steam

by LARRY HANOVER

IN 1993, THE NATIONAL INSTITUTES of Health (NIH) Revitalization Act mandated that women and members of racial and ethnic minorities be recruited for all NIH-sponsored clinical trials, with enough participants in subpopulations, particularly in phase 3 studies, to assess any valid differences in outcomes. Investigators seeking NIH grants were required to conduct outreach programs to help ensure that those goals were met.1

But when it comes to minorities with cancer, the law has failed to deliver on its promise. Nearly 30 years after NIH sought to increase participation of minorities in clinical trials, a demographic imbalance remains. Of 4922 patients who participated in clinical trials that led to approvals for 18 new oncology drugs during 2020, 73% were White, 14% were Asian, 6% were Hispanic, and 5% were Black or African American, according to the FDA (FIGURE).2

During the past year, however, the COVID-19 pandemic has shined a new light on health care disparities while racial justice protests have added an element of intensity to the discussions, experts say. A recent spate of developments illustrates fresh momentum for broadening access to clinical trials—and cancer care overall—for Black and Hispanic patients as well as other populations with lagging participation. These developments include the following:

• A “road map” for designing multiple myeloma (MM) clinical trials that include more African American patients has been advanced by investigators from the Dana-Farber Cancer Institute in Boston, Massachusetts, in collaboration with experts from the FDA and the American Association for Cancer Research (AACR).3
  The plan follows study findings that show the number of African American individuals enrolled in select MM trials declined by 3.5% from 2002 to 2011, even though incidence and mortality rates for the malignancy are higher than they are for White patients.4

• A massive COVID-19 relief and government funding package that Congress passed in December 2020 will require state Medicaid programs to cover routine patient costs for participation in qualifying clinical trials, including for cancer indications, starting in 2022. The lack of Medicaid coverage has impeded recruitment of minorities and the poor.5

• In September 2020, AACR released its first comprehensive report, which describes health care inequities and serves as a call to action for patients with cancer, including expanding clinical trial enrollment among minorities.6

• New models for improving access to clinical trials for minorities include hospital partnerships with community centers and clinical practices to treat patients in the areas where they live to increase clinical trial participation.

In interviews with OncologyLive®, leading oncology experts say that the convergence of efforts represents progress for racial minorities and that, they believe, this time there will be no turning back.

“I think it’s changed,” said Kimlin Tam Ashing, PhD, founding director of the Center of Community Alliance for Research and Education and professor in...
the Department of Population Sciences at City of Hope Medical Center in Duarte, California. “I think it’s multiple factors, particularly the Black Lives Matter movement and COVID-19. I think the whole country, the whole world has come to a deeper consciousness-raising and the sense that we have to do something. We cannot ignore this and say this is somebody else’s responsibility.”

**COVID-19 HIGHLIGHTS PROBLEMS**
The death toll from COVID-19 in the United States has surpassed the 570,000 mark, but the disproportionate impact on minorities is pronounced. The risk of COVID-19 hospitalization and death is 2.8 and 1.9 times higher, respectively, for Black or African American non-Hispanic individuals than it is for White individuals and 3.0 and 2.3 times higher, respectively, for Hispanic or Latino persons. “Race and ethnicity are risk markers for other underlying conditions that affect health, including socioeconomic status, access to health care, and exposure to the virus related to occupation, eg, frontline, essential, and critical infrastructure workers,” according to the CDC. 7

Such statistics cast renewed attention on disparities in cancer care. Overall, progress has been made in narrowing the gap in the cancer death rate, which was 33% higher in 1990 for African American vs White individuals to 14% higher in 2016, according to the AACR report; but much work remains to be done. 6 The risk of dying from prostate cancer is 111% higher for African American men than it is for White men, and African American women have a 39% higher risk of dying from breast cancer than White women. Also, when it comes to leukemia, Hispanic children and adolescents are 20% and 38% more likely to develop the disease, respectively, than White children and adolescents. 6

The task of making clinical trial populations more inclusive is complicated by a variety of factors, including trial availability, restrictive eligibility criteria, and the logistics of taking time off from work, the AACR report noted. 6

Moreover, concerns about inclusion of racial minorities in clinical trials are played out against a backdrop of broader issues about the gap between study populations and real-world patients with cancer. One study found that enrollment in a clinical trial for first-line therapy markedly favors patients who are younger and have fewer comorbidities than the population of patients with cancer as a whole, as well as those with private insurance, and those who obtain treatment at academic medical centers. 8

In some respects, the disparities in clinical trial enrollment are a result of business pressures that drive pharmaceutical companies to test novel drugs in homogenous populations with fewer confounding factors at high-enrolling sites. 9

Additionally, the increasingly global nature of oncology drug development may worsen the minority enrollment gap in the United States, investigators found. In a study of patient enrollment in 49 global trials supporting 35 FDA drug approvals from 2015 through 2018 with race data available, Black patients made up only 2.5% of participants (range, 0%-10%). In 21 trials with both race and accrual location data available, 64% of patients were from outside the United States. 10

**NEW MODEL FOR MM RESEARCH**
One of the more concrete proposals aimed at improving racial imbalances in clinical trials is getting underway in the MM research community as leading investigators seek to extend the benefits of novel treatments to underrepresented populations.

“We’ve had a paradigm shift and a marked improvement in outcomes of patients due to the development of multiple novel treatments,” Kenneth C. Anderson, MD, a 2014 Giants of Cancer Care® award winner in the myeloma category, said in an interview. “It turns out not all patients have shared equally in the progress.”

Compared with White individuals, African American persons are more than twice as likely to receive a diagnosis of MM (15.9 vs 7.5 cases per 100,000 population) and to die from the disease (5.6 vs 2.4 myeloma deaths per 100,000). From 1973 to 2005, the 5-year relative survival rate increased from 26.3% to 35.0% for White Americans, a statistically significant improvement (P < .005), compared with an increase from 31.0% to 34.1% for African American people. An analysis of

**FIGURE. 2020 Clinical Trials Snapshot for New Oncology Drugs**

Demographics of trials for 18 new drugs approved by the FDA

- 73% were women.
- 44% were 65 years and older.
- 41% were from sites outside the United States.
- 61% were White patients.
- 14% were Hispanic patients.
- 5% were Black or African American patients.
- 14% were Asian patients.
- 6% were women.

KENNETH C. ANDERSON, MD
9 large MM trials conducted by National Cancer Institute cooperative groups showed that enrollment of African American participants declined to 13% during 2002 to 2011 from 16.5% in the prior decade.6

Findings from other studies show that a more racially diverse trial population may yield a different outcome. For example, patients with MM of high African ancestry are more likely than those with high European background to harbor immunoglobulin heavy-chain translocations on chromosome 14, specifically t(11;14) and the high-risk t(14;16) or t(14;20) abnormalities.4

This could have therapeutic implications for patients. In the phase 3 BELLINI trial (NCT02755597), the benefit of adding venetoclax (Venclexta) vs placebo to bortezomib (Velcade) and dexamethasone in patients with relapsed or refractory MM was observed only in those participants with t(11;14) and high BCL2 expression.11

Anderson, who is studying venetoclax in patients with MM and t(11;14), sees the biomarker-driven emphasis as a noteworthy implication of more diverse clinical trial populations. “That’s a major opportunity to carry out clinical trials of this novel agent that are solely or certainly enriched by African American patients,” said Anderson, the Kraft Family Professor of Medicine at Harvard Medical School and director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics at Dana-Farber Cancer Institute.

New recommendations to make MM trials more racially inclusive grew out of a workshop involving Anderson, who heads the AACR’s regulatory science and policy subcommittee, and FDA officials.

Before clinical trials are approved, sponsors should consider expanding cohorts with broader eligibility criteria, drafting a specific diversity study plan, appointing a diversity officer for phase 2 and 3 studies, and designing trials that cover disease subtypes and features most commonly seen in African American individuals.4

The plan, which also includes postapproval recommendations, could be applied to other groups and diseases, investigators noted. “Indeed, it is the hope of everyone who contributed to this initiative that these recommendations will lead to a more inclusive, ‘real world’ drug development paradigm,” the authors wrote.9

### DIVERSITY AFFECTS FINDINGS

Underrepresentation of minorities in clinical trials comes at the cost of not knowing whether treatment effectiveness and adverse effects are the same for their populations as for White patients. For instance, the patient’s immune status is believed to have an impact on the efficacy of immunotherapy. However, a recent analysis showed that the percentage of Black or African American patients ranged from 0% to 4% in clinical trials that led to approvals of immune checkpoint inhibitors involving 6 cancer types.9

Additionally, disparities for minority participation have significant overlap with imbalances for other subgroups. In a study of outcomes for 41,109 patients who participated in large phase 2 and phase 3 trials from 1985 to 2012, participants from areas with the highest socioeconomic deprivation had worse outcomes compared with those from the most affluent areas for overall survival (HR, 1.28; 95% CI, 1.20-1.37; P < .001), progression-free survival (HR, 1.20; 95% CI, 1.13-1.28; P < .001), and cancer-specific survival (HR, 1.27; 95% CI, 1.18-1.37; P < .001).12

Such findings illustrate why it was so critical for legislation requiring Medicaid to cover routine costs for patients participating in clinical trials, said Karen Winkfield, MD, PhD, who recently was named executive director of the Meharry-Vanderbilt Alliance, a strategic partnership between Meharry Medical College, a historically Black institution, and Vanderbilt University Medical Center, both in Nashville, Tennessee. “This is not just race-ethnicity,” Winkfield said in an interview. “This is poor people, rural people.”

The AACR report used contributions from experts throughout the oncologic field to propose a blueprint for addressing health disparities. Among the recommendations were improving minority representation in clinical trial enrollment—including reduction of certain restrictive eligibility criteria—improving screening and early detection of cancers, conducting diversity-focused training and career development programs, and increasing diversity within the clinician pool.6

Years of underrepresentation of African American and Hispanic participants in clinical trials has taken a cumulative toll as far as lack of data on how they might be affected by certain treatments. A 2009 analysis found that, despite the requirements of the NIH Revitalization Act of 1993, racial and ethnic groups were scarcely represented in genomic studies: 96% were carried out in populations

---

**TABLE. Recommendations for Expanding Clinical Trial Eligibility**

<table>
<thead>
<tr>
<th>Criteria addressed in new ASCO/Friends of Cancer Research report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Washout periods</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
</tr>
<tr>
<td><strong>Laboratory reference ranges and test intervals</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
</tr>
</tbody>
</table>

ASCO, American Society of Clinical Oncology; PS, performance status.
of European descent. Although samples in the proportion of genome-wide association studies from underrepresented populations had risen to 19% when the issue was revisited in 2016, most of the increase was from Asian ancestry samples, with other ethnic groups experiencing minimal increase (from 1% to 4%).

“There’s so much we need to learn in this area,” said Edith A. Perez, MD, the 2014 Giants of Cancer Care® award winner in the community outreach category, the Serene M. and Frances C. Durling Professor of Medicine at Mayo Clinic College of Medicine in Jacksonville, Florida, and vice chair of the Alliance for Clinical Trials in Oncology. “But the good thing is that the increased discussion in this topic is directly translating into action like I don’t remember seeing in the past.”

Broadening eligibility criteria overall is another key strategy to improve participation of minorities in clinical trials. In February, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research issued new recommendations in 5 specific areas: treatment washout periods, comorbidities, laboratory reference ranges and test intervals, and patient performance status (TABLE14). The groups’ previous effort to expand trial eligibility resulted in the FDA revising its guidance for patients with brain metastases, minimum age for enrollment, HIV status, organ dysfunction, and prior or concurrent malignancies.14

“Clinical trial access must be recognized as a health equity issue,” Lori J. Pierce, MD, FASTRO, FASCO, a professor and vice provost for academic and faculty affairs at the University of Michigan who is president of ASCO, said in announcing the new recommendations. “Overly restrictive eligibility criteria without scientific justification has led to an underrepresentation of older adults, racial/ethnic and sexual/gender minorities, and patients with well-managed comorbidities.”14

More focus should be placed on needlessly excluding patients due to comorbidities, Perez said. “Patients are being excluded for various reasons, including age, because it’s associated with comorbidities and concern about their impact and safety,” she said. “But we’ve learned those factors are really irrelevant.”

**SOME CENTERS REPORT CHANGE**

A paper published last year in *Contemporary Clinical Trials Communications* by Jeanne M. Regnante, chief health equity and diversity officer at the LUNGevity Foundation in Bethesda, Maryland, and colleagues illustrates a path forward on improving diversity.

Fourteen leaders representing 8 cancer centers were asked how they achieved accrual rates for racial and ethnic minority groups of 10% to 50% in a 12-month reporting period. Among the findings were metrics for collection and reporting, routinely captured race and ethnicity data that are accessible to staff, and operational standards to support access and inclusion.15

“I think when it becomes part of your standard practice, you don’t overthink,” Winkfield said. “You don’t say, ‘Oh, this is a Black person, and it’s going to be harder and they’re going to have issues.’ Or if you have a Spanish-speaking person, you don’t say, ‘Oh, it’s going to really tough. We’ve got to go get a translator.’”

The percentages of African American and Hispanic participants in trials for COVID-19 vaccines have been much more representative of the actual population, Winkfield noted. Outreach is critical to the African American community partly because of the Tuskegee Study of Untreated Syphilis in the Negro Male, in which hundreds of Black men were not given penicillin for the infection as part of a study even after it was established as a cure. The study continued for 40 years before being halted in 1972.16

According to the CDC, Pfizer/BioNTech and Moderna, Inc had approximately 10% Black representation in their trials and 26.2% and 20.0% Hispanic representation, respectively. As of 2019, according to the US Census Bureau, 12.3% and 17.6% of the population 16 years and older were Black persons and Hispanic persons, respectively.17

Ashing said clinicians’ frame of reference on Black patients’ reticence to participate in trials also needs to change. “Much of the literature from media and scientific literature describes this as medical mistrust,” she said. “I refrain from that terminology because I believe it is victim blaming. I prefer to frame it in terms of adaptive caution and concern because of our history of medical abuse.”

Some hospitals are taking innovative steps to reach out to the community, Ashing noted. City of Hope is developing partnerships with community clinics and hospitals as well as through their 29 community practices. These practices were developed in areas with high minority density and high numbers of underserved patients with cancer to provide access for prevention, screening, and studies and clinical trials. The use of telemedicine, brought about by the pandemic, may make significant inroads as well, she said.

Winkfield said the recruitment of racial and ethnic minorities to oncology teams is crucial. Patients feel more comfortable with doctors who look like them, she said. “What I usually get from Black patients is, ‘Oh my God, I can’t believe you’re a Black doctor.’ It’s different. There’s an instant rapport. I may be the first Black doctor they’ve ever seen.”

When White oncologists are not culturally aware and respectful enough of minority patients, the results can be tragic, Winkfield said. She described the case of a 28-year-old Black nurse with triple-negative breast cancer, the incidence of which is disproportionately higher in African American women. Winkfield advised her to undergo chemotherapy first and then surgery and radiation.

At their next visit, the woman explained to Winkfield that she had stopped the chemotherapy due to adverse effects and had gone straight to surgery. Winkfield said the oncologist, who was a White physician, dismissed the woman’s concerns rather than prescribe medication for the adverse effects and agreed to let her halt chemotherapy instead of insisting she stay the course.

Winkfield directed the woman back to chemotherapy, but it was too late. “I can’t say it was a direct result of the fact that she [went months without] chemotherapy, but that young woman ended up dying of brain metastases at age 29,” Winkfield said. “Those sorts of stories should never happen.”

---

**For a full list of references, see the article at **[OncLive.com](https://www.OncLive.com)
NEW to decrease the incidence of chemotherapy-induced myelosuppression in patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen

FOR EXTENSIVE-STAGE SMALL CELL LUNG CANCER (ES-SCLC)

SPARE THE MARROW.
COSELA HELPS PROTECT AGAINST MYELOSUPPRESSION,

COSELA™ (trilaciclib) helps protect hematopoietic stem and progenitor cells (HSPCs), the source of blood cell lineages

FDA BREAKTHROUGH THERAPY DESIGNATION

PROACTIVELY HELP PROTECT AGAINST MULTIPLE MYELOSUPPRESSIVE CONSEQUENCES WITH THE FIRST AND ONLY MYELOPROTECTION THERAPY

The Pivotal Study (Study 1) compared an etoposide/carboplatin + atezolizumab (E/P/A) regimen with COSELA vs without COSELA*

INDICATION

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

*COSELA was evaluated in 3 randomized, double-blind, placebo-controlled clinical studies. The Pivotal Study (Study 1) evaluated COSELA or placebo administered prior to treatment with E/P/A in 107 patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. In this study, COSELA significantly reduced the primary endpoints of incidence (adjusted relative risk [aRR] 0.038 [95% CI, 0.008, 0.195], P<0.0001) and duration in Cycle 1 (mean difference -3.8 [95% CI, -4.9, -2.3], P<0.0001) of severe neutropenia and significantly decreased the rate of all-cause chemotherapy dose reductions (aRR 0.242 [95% CI, 0.079, 0.742]). The incidence of Grade 3/4 anemia was 19% and 28% (aRR 0.663 [95% CI, 0.336, 1.310]) and RBC transfusions on/after 5 weeks difference -3.6 [95% CI, -4.9, -2.3], P<0.0001) of severe neutropenia and significantly decreased the rate of all-cause chemotherapy dose reductions (aRR 0.242 [95% CI, 0.079, 0.742]). The incidence of Grade 3/4 anemia was 19% and 28% (aRR 0.663 [95% CI, 0.336, 1.310]) and RBC transfusions on/after 5 weeks

NOW APPROVED


G1 Therapeutics™ and the G1 Therapeutics logo, COSELA™ and the COSELA logo are trademarks of G1 Therapeutics, Inc. ©2021 G1 Therapeutics, Inc. All rights reserved. US-2000037 03/2021
SPARE THE MARROW.
WHILE CHEMOTHERAPY TARGETS CANCER CELLS

SELECT IMPORTANT SAFETY INFORMATION

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

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

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

Interstitial Lung Disease/Pneumonitis
- Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, including COSELA, with which it occurred in 1 (0.4%) of 272 patients receiving COSELA in clinical trials. Monitor patients for pulmonary symptoms of ILD/pneumonitis. For recurrent moderate (Grade 2) ILD/pneumonitis, and severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

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

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

To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-G1TX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This information is not comprehensive. Please see the Brief Summary of Prescribing Information on the adjacent page.
**CONTRAINdications**

COSELA™ (trilaciclib) is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib. Reactivation of varicella-zoster virus is a contraindication [see Warnings and Precautions (5.2)].

**WARNINGS AND PRECAUTIONS**

**Injection-Site Reactions, Including Phlebitis and Thrombophlebitis**

COSELA® (trilaciclib) for injection, for intravenous use

**Dose Modification for Adverse Reactions**

**Acute drug hypersensitivity reactions**

**Relevant Dosing Regimen**

If COSELA is discontinued, wait 96 hours from the last dose of COSELA before resuming chemotherapy.

**Table 1: Recommended Actions for Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity Grade</th>
<th>Recommended Action</th>
</tr>
</thead>
</table>
| Grade 1: Tenderness or pain without symptoms (e.g., warmth, erythema, itching) | None | Continue 

**Adverse Reactions**

The safety of COSELA was assessed in Studies 1, 2, and 3 (Clinical Studies) (14 Patients) Patients received COSELA 240 mg/m² by 30-minute intravenous infusion prior to chemotherapy on each day chemotherapy. The data described in this section reflect exposure to COSELA among 240 patients (122 patients in the trilaciclib group and 118 patients in the placebo group) receiving for extended phase small cell lung cancer (ES-SCLC) in 3 randomized, double-blind, placebo-controlled trials: 32 patients with trilaciclib and isosulfan BL (ES-SCLC) concurrently treated with cisplatin and etoposide (VP-16) or with cisplatin (ES-SCLC) treated previously with trilaciclib. The data presented below are for the 105 patients who received study treatment.

**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 compared directly with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. A grade 2 hypokalemia was observed in 10% of patients.

**Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization may be indicated; disabling, but not self-care ADL.**

**Grade 4: Life-threatening; hospitalization required; irreversible consequences; urgent medical intervention indicated.**

**Dose modification**

If the COSELA dose is missed, discontinue chemotherapy on the day the COSELA dose was missed. If COSELA is discontinued, wait 96 hours from the last dose of COSELA before resuming chemotherapy.

**Acute drug hypersensitivity reactions**

If Grade 2 recurs, permanently discontinue COSELA. If Grade 2 recurs, discontinue chemotherapy on day 28 and the drug is resumed on day 31. If Grade 2 recurs, patients receiving COSELA and 1% receiving placebo completed 4 cycles of induction therapy. Patients with ES-SCLC enrolled in Study 1 (NCT02178057; G1T28-02) were randomized (2:1), double-blind, placebo-controlled (2:1) to receive COSELA or placebo as an intravenous (IV) infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy was administered. The interval between doses of COSELA as a sequential daily should not be greater than 28 hours.

**Drug Interactions**

Effect of Other Drugs. Certain, C02T2, N.11, and MATE 2K Substrates COSELA is an inhibitor of C02T2, MATE 1, and MATE 2-K substrates. COSELA may increase the concentration of net accumulation of C02T2, MATE 1, and MATE 2-K substrates in the kidney (i.e., enterohepatic recycling).

**Dosage and Administration**

**Accurate Drug Information**

The safety of COSELA was evaluated in Studies 1, 2, and 3 (Clinical Studies) (14 Patients) Patients received COSELA 240 mg/m² by 30-minute intravenous infusion prior to chemotherapy in each day chemotherapy. The data described in this section reflect exposure to COSELA among 240 patients (122 patients in the trilaciclib group and 118 patients in the placebo group) receiving for extended phase small cell lung cancer (ES-SCLC) in 3 randomized, double-blind, placebo-controlled trials: 32 patients with trilaciclib and isosulfan BL (ES-SCLC) concurrently treated with cisplatin and etoposide (VP-16) or with cisplatin (ES-SCLC) treated previously with trilaciclib. The data presented below are for the 105 patients who received study treatment. Eighty-five percent of patients receiving COSELA and 1% receiving placebo completed 4 cycles of induction therapy. Patients with ES-SCLC enrolled in Study 1 (NCT02178057; G1T28-02) were randomized (2:1), double-blind, placebo-controlled (2:1) to receive COSELA or placebo as an intravenous (IV) infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy was administered. The interval between doses of COSELA as a sequential daily should not be greater than 28 hours.
Immune-Based Treatments Crowd Metastatic RCC Paradigm

by JESSICA HERGERT

THE EMERGENCE OF MULTIPLE combination regimens with immunotherapy and tyrosine kinase inhibitors (TKIs) has been welcome for the frontline treatment of patients with metastatic renal cell carcinoma (mRCC); however, without head-to-head comparative data, treatment selection has become individualized based on available patient characteristics. Those patients deemed eligible for immunotherapy are then further stratified to either standard-of-care combination regimens or to single-agent immunotherapy, an increasingly less common approach, said Primo Nery Lara Jr, MD, in a virtual presentation during the New York GU™ 14th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies, a program hosted by Physicians’ Education Resource®, LLC (PER®).1

“[Next], address that patient’s eligibility for immunotherapy. Immune-based combination therapies [are] the standard of care in 2021, but you will consider some subset of patients for monotherapy, whether with an immunotherapy agent or a VEGFR [-directed] TKI,” Lara added.

Risk stratification should be considered prior to making any treatment-related decisions, because some patients may be eligible for active surveillance, said Lara. Additionally, risk score, per the International Metastatic RCC Database Consortium, can inform eligibility for cytoreductive nephrectomy (FIGURE 1).

“The decision [of whether to pursue cytoreductive nephrectomy] must be individualized to the patient according to risk of recurrence, regression, and death,” Lara said. “Most favorable-risk patients and some intermediate-risk patients remain candidates for cytoreduction, especially those who have large and/or symptomatic tumors with low-volume metastatic disease.”

Highly selected patients may also be candidates for metastasectomy. Although data are mostly limited to retrospective studies, patients with good performance status who have isolated or oligometastatic disease, a disease-free interval of longer than 2 years post nephrectomy, no lymph node involvement, and/or lung-only disease may benefit from metastasectomy.

COMBINATION VS SINGLE AGENTS

Lara explained that it is important to recognize which patients are not eligible for immune-based therapies, including those with active autoimmune disease who are likely to develop unacceptable toxicity from immunotherapy. Other patients who should not receive immunotherapy are those with a history of solid organ transplantation, those receiving supraphysiologic corticosteroids or chronic immunosuppressive therapy, and those whose have a personal preference against intravenous treatment administration.

If a patient is indicated as a candidate for immunotherapy, nuanced treatment selection is needed to determine whether a single-agent or combination regimen is optimal, Lara said.

“Monotherapy has its advantages. It is lower-cost, simpler, and better tolerated than combination therapy. [It also] offers a reduced risk of drug-drug interactions, and, by the mere fact that only 1 drug is being given, adherence is likely to be higher,” said Lara.

Historically, the frontline mRCC paradigm was dominated by single-agent angiogenesis...
inhibitors, such as sunitinib (Sutent), pazopanib (Votrient), cabozantinib (Cabometyx), axitinib (Inlyta), sorafenib (Nexavar), and bevacizumab (Avastin). However, the field expanded rapidly in recent years to favor combination regimens as standard frontline options.

Across all risk groups, combinations of immunotherapy and TKIs including pembrolizumab (Keytruda)/axitinib, nivolumab (Opdivo)/cabozantinib, pembrolizumab/lenvatinib (Lenvima), and avelumab (Bavencio)/axitinib, have demonstrated activity in patients with RCC compared with sunitinib alone.

The combination of cabozantinib and nivolumab, which was approved by the FDA on January 22, 2021 for the frontline treatment of patients with advanced RCC, demonstrated a 49% reduction in the risk of disease progression or death compared with sunitinib.\(^2\)

Data from CheckMate 9ER (NCT03141177) demonstrated that the combination elicited a median progression-free survival (PFS) of 16.6 months (95% CI, 12.5-24.9) vs 8.3 months (95% CI, 7.0-9.7) with sunitinib (HR, 0.51; 95% CI, 0.41-0.64; \(P<.0001\)). At a median follow-up of 10.6 months, the median overall survival (OS) was not reached (NR) in either arm but a 40% reduction in the risk of death was demonstrated with the combination (HR, 0.60; 95% CI, 0.40-0.89; \(P = .0010\)).

Most recently, findings from the phase 3 CLEAR trial (NCT02811861), presented during the 2021 Genitourinary Cancers Symposium, demonstrated an improvement in OS, PFS, and overall response rate (ORR) with the combination of frontline lenvatinib and pembrolizumab vs sunitinib in patients with advanced RCC.\(^3\)

Although the combination is not yet approved for patients with RCC, results showed that the median PFS was 23.9 months (95% CI, 20.8-27.7) with the combination compared with 9.2 months (95% CI, 6.0-11.0) with sunitinib. The median OS was NR in either arm but a 34% reduction in the risk of death was seen with the combination vs sunitinib (HR, 0.66; 95% CI, 0.49-0.88; \(P = .005\)).

Data also demonstrated improved PFS and ORR, but not OS, with the combination of lenvatinib plus everolimus (Afinitor) vs sunitinib.

Another approved frontline option for patients is the immunotherapy doublet of nivolumab plus ipilimumab (Yervoy), for patients with intermediate- or poor-risk disease.\(^4\)

**OTHER OPTIONS TO CONSIDER**

Frontline checkpoint inhibitor monotherapy with either pembrolizumab or nivolumab may be considered in select patients who are ineligible for or refuse VEGFR-directed TKI-containing combinations or who are averse to ipilimumab. Single-agent pembrolizumab has demonstrated an ORR of 33.6% (95% CI, 24.8%-43.4%) and a median PFS of 6.9 months (95% CI, 5.1-NR) in patients \(n = 110\) with mRCC.\(^5\)

Nivolumab monotherapy demonstrated an ORR of 31.7% (95% CI, 27.4%-46.1%) and a median PFS of 8.3 months (95% CI, 5.5-10.9) in patients with mRCC \(n = 123\).\(^6\)

Alternatively, VEGFR-directed TKI monotherapy with cabozantinib may be considered for certain patients who are ineligible for, intolerant of, or refuse immunotherapy.

Data from the open-label phase 2 PAPMET SWOG S1500 trial (NCT02761057) were presented during the 2021 Genitourinary Cancers Symposium. The trial randomized patients with metastatic papillary RCC who had 0 or 1 prior line of therapy that was not sunitinib to receive single-agent sunitinib, cabozantinib, crizotinib (Xalkor), or savolitinib. The median PFS was 9.0 months with cabozantinib, 2.8 months with crizotinib, 3.0 months with savolitinib, and 5.6 months with sunitinib, showing that cabozantinib monotherapy was superior to sunitinib in this patient population (HR, 0.60; 95% CI, 0.37-0.97; \(P = .019\)).\(^7\)

Other treatment considerations for frontline therapy include high-dose interleukin-2 (IL-2) monotherapy and mTOR inhibitor monotherapy; however, these options are reserved for a very limited number of patients. High-dose IL-2 may be used in robust patients with excellent performance status and normal end-organ function, but it requires inpatient treatment and is associated with significant toxicity. mTOR inhibitors, such as temsirolimus (Torisel), have lost their place in the landscape for the treatment of patients with poor-risk mRCC.

“Temsirolimus was originally tested in a registration trial in a poor-risk context using composite criteria, but in the era of more active, life-prolonging therapies, there is very little justification for routine temsirolimus use,” Lara said.

For a full list of references, see the article at bit.ly/3enZIER.
**PARP Inhibitors, Novel Combos Represent the Future in mCRPC**

*by JASON HARRIS*

The treatment paradigm for patients with metastatic castration-resistant prostate cancer (mCRPC), novel strategies targeting the androgen receptor (AR) should be at the forefront of research efforts, according to William K. Kelly, DO.

IN ORDER TO ADVANCE the treatment paradigm for patients with metastatic castration-resistant prostate cancer (mCRPC), novel strategies targeting the androgen receptor (AR) should be at the forefront of research efforts, according to William K. Kelly, DO.

Investigators have identified molecular changes that occur when a patient’s disease progresses from a castration-sensitive state to a castration-resistant state, which has helped drive advances in therapeutic options, Kelly said in a presentation during the New York GU™ Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies.

“This gave opportunities for investigators to look at these pathways and develop new targets for these alterations,” said Kelly, a professor of medical oncology and urology at Thomas Jefferson University and director of the Division of the Solid Tumor Oncology at Sidney Kimmel Cancer Center at Jefferson Health, both in Philadelphia.

PARPS JOIN THE LINEUP

Study findings have shown that the frequency of DNA repair alterations increases as prostate cancer progresses; an estimated 19% to 23% of patients with mCRPC harbor mutations in this pathway, Kelly said.

PARP activity is essential for the repair of single-strand DNA breaks, and PARP inhibitors target aberrant DNA repair mechanisms. Kelly said these agents induce “synthetic lethality,” which occurs between 2 genes when a cell can survive mutation in 1 gene but not simultaneous mutation in both. Identification and mechanistic characterization of genetic interactions are key to exploiting synthetic lethality in cancer treatment.

“PARPs repair single-stranded breaks in normal patient DNA repair,” Kelly said. “With PARP inhibitors, single-strand breaks convert to double-strand breaks. Patients with BRCA mutations, what we call HRR [homologous recombination repair] deficient, won’t repair these double-stranded breaks and the cell goes on to apoptosis.”

PARP inhibitors entered the treatment landscape last year when the FDA approved 2 agents for patients with mCRPC within a week. On May 15, 2020, rucaparib (Rubraca) became the first biomarker-driven targeted therapy for the malignancy when the FDA granted an accelerated approval for its use in patients with BRCA-mutant mCRPC (germline and/or somatic) who received prior AR-directed therapy and taxane-based chemotherapy.

Rucaparib was approved based on findings from the single-arm phase 2 TRITON2 trial (NCT02952534), in which monotherapy with the PARP inhibitor resulted in a confirmed objective response rate (ORR) of 43.5% (95% CI, 31.0%-56.7%) by independent review, with 7 (11.3%) complete responses and 20 (32.3%) partial responses. The confirmed ORR by investigator assessment was 50.8% (95% CI, 38.1%-63.4%).

Final approval for rucaparib is contingent on the results of the phase 3 TRITON3 trial (NCT02975934), which is seeking to recruit 400 patients with mCRPC harboring a BRCA1/2 or ATM mutation that has progressed after 1 prior line of therapy with a next-generation AR-targeting therapy.

Four days after rucaparib was approved, olaparib (Lynparza) gained a new indication for treating patients with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including BRCA, which have progressed following treatment with enzalutamide (Xtandi) or abiraterone acetate (Zytiga); this is based on findings from the phase 3 PROfound trial (NCT02987543).

In PROfound, investigators determined that olaparib monotherapy was superior to prednisone plus either enzalutamide or abiraterone for patients with mCRPC who had tumors with at least 1 alteration in BRCA1, BRCA2, or ATM (cohort A) or in any of 12 HRR genes (cohort B). The study population included 387 patients who had disease progression on prior hormone-targeting agents.

In cohort A, the median radiologic progression-free survival (rPFS), the primary end point of the study, was 7.4 months (95% CI, 6.2-9.3) for those who received olaparib vs 3.6 months (95% CI, 1.9-3.7) for those who received physician’s choice of standard therapy, which translated into a 66% reduction in the risk of disease progression or death (HR, 0.34; 95% CI, 0.25-0.47; P < .0001). In cohorts A plus B, median rPFS was 5.8 months for olaparib (95% CI, 5.5-7.4) vs 3.5 months (95% CI, 2.2-3.7), resulting in an HR of 0.49 (95% CI, 0.38-0.63; P < .0001).

Olaparib also demonstrated an improvement in median overall survival (OS). In cohort A, the median OS was 19.1 months (95% CI, 17.4-23.4) with olaparib vs 14.7 months (95% CI, 11.9-18.8) for physician’s choice of therapy (HR, 0.69; 0.50-0.97; P = .02). In the combined populations of cohorts A and B, the median OS was 17.3 months (95% CI, 15.5-18.6) vs 14.0 months (95% CI, 11.5-17.1) for olaparib and physician’s choice, respectively, translating into an HR of 0.79 (95% CI, 0.51-1.03).

Kelly added that new data presented at the 2021 Genitourinary Cancers Symposium showed that patients with ATM and CDK12 mutations also exhibit significant response to olaparib. “Those are another subset of patients who we need to understand and possibly treat in the future,” he said.

WHAT COMES NEXT?

In addition to PARP inhibitor studies, the treatment landscape is being shaped by trials that explore therapies in combination or in sequence. “Therapeutic options for mCRPC have greatly expanded over the years,” Kelly said. “So, really, the questions are: What comes next? How do we actually pick the order [of treatments]? Or are there better combinations?”

Of note, the efficacy of cabazitaxel (jevtana), a taxane chemotherapy, was established in the setting of recurring mCRPC in the phase 4 CARD trial (NCT02485691)
Conference Highlights

NEW YORK GU™

in patients who had previously received
docetaxel and progressed within 1 year of
receiving either enzalutamide or abiraterone. Participants were randomized to receive
cabazitaxel plus prednisone and granulocyte
colonystimulating factor vs abiraterone plus
prednisone.

Patients who received cabazitaxel
had a median imaging-based PFS of 8.0
months (95% CI, 5.7-9.2) vs 3.7 months
(95% CI, 2.8-5.1) for those who received
an antiandrogen (HR, 0.54; 95% CI, 0.40-
0.73; P < .001). The secondary end point of
median OS was 13.6 months (95% CI, 11.5-
17.5) with cabazitaxel vs 11.0 months (95%
CI, 0.46-0.89; P = .008).6

“The quality-of-life measures were better
all the way through with cabazitaxel vs
another AR-directed therapy,” Kelly added.

“Pain response was significantly better
with the use of cabazitaxel, 45.0% vs
19.3%. Probability of no pain progression
was also improved with chemotherapy vs
abiraterone or enzalutamide, which really
starts defining that chemotherapy still has
a role in patients with mCRPC.”

In the phase 3 ACIS trial (NCT02257736),
investigators found that adding apalutamide
(Erleada), an AR inhibitor, to abiraterone
plus prednisone reduced the risk of radio-
graphic progression or death by 30% in
patients with chemotherapy-naive mCRPC
receiving androgen deprivation therapy.

At a median follow-up of 54.8 months,
the median rPFS was 24.0 months in the
apalutamide arm compared with 16.6
months with placebo plus abiraterone and
prednisone (HR, 0.70; 95% CI, 0.60-0.83).
OS in the combination arm was 36.2 vs
33.7 months in the control arm (HR, 0.95;
95% CI, 0.81-1.11; P = .498).9

The findings met the primary end point
of the study, but the combination did not
significantly improve OS vs the control,
Kelly noted. He said subgroup analyses may
provide further information about which
patients could benefit from the approach.

Meanwhile, a variety of novel strategies
are being explored (TABLE). “There are
multiple other opportunities for AR-targeted
therapies,” Kelly said. “[Trials of] multiple
new agents are going to be reporting out that
look at different targets, from EZH2 to BET
inhibitors to transcription coactivators such
as CBP and p300, inhibitors that have
unique actions. We look forward to [data
from] those trials coming out.”

TABLE. Ongoing Development of Select AR-Targeting Combinations and Strategies in mCRPC by Mechanism of Action

<table>
<thead>
<tr>
<th>Agent</th>
<th>Ongoing trial</th>
<th>Setting</th>
<th>Phase</th>
<th>Trial identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcriptional co-activator CBP/P300 inhibitor</td>
<td></td>
<td>mCRPC (expansion phase in patients with advanced solid tumors with molecular markers which may indicate potential for response to p300/CBP inhibition)</td>
<td>1/2</td>
<td>NCT03568656</td>
</tr>
<tr>
<td>CS1477</td>
<td>monotherapy or in combination with enzalutamide or abiraterone</td>
<td>mCRPC</td>
<td>1/2</td>
<td>ProSTAR; NCT03480646</td>
</tr>
<tr>
<td>EZH2 inhibitor</td>
<td></td>
<td>mCRPC</td>
<td>1</td>
<td>NCT03150056</td>
</tr>
<tr>
<td>CPI-1205</td>
<td>+ enzalutamide or abiraterone/prednisone</td>
<td>CRPC</td>
<td>3</td>
<td>IPATential150; NCT03072238</td>
</tr>
<tr>
<td>BET inhibitor</td>
<td></td>
<td>mCRPC</td>
<td>1</td>
<td>NCT02833883</td>
</tr>
<tr>
<td>AKT inhibitor</td>
<td></td>
<td>mCRPC</td>
<td>1</td>
<td>NCT02987829</td>
</tr>
<tr>
<td>Ipatasertib</td>
<td>+ abiraterone vs placebo + abiraterone</td>
<td>mCRPC</td>
<td>1/2</td>
<td>NCT02566772</td>
</tr>
<tr>
<td>Dual mTOR/DNAPK inhibitor</td>
<td></td>
<td>mCRPC</td>
<td>1</td>
<td>NCT02566772</td>
</tr>
<tr>
<td>CC-115</td>
<td>+ enzalutamide</td>
<td>mCRPC</td>
<td>1</td>
<td>NCT03437941</td>
</tr>
<tr>
<td>AR antagonist with specific activity against F877L</td>
<td></td>
<td>mCRPC; adenocarcinoma, prostate</td>
<td>1/2</td>
<td>NCT03480646</td>
</tr>
<tr>
<td>TRC253</td>
<td>monotherapy</td>
<td>mCRPC</td>
<td>1/2</td>
<td>NCT02566772</td>
</tr>
<tr>
<td>Pure AR antagonism plus down-regulation of full-length and splice variant AR</td>
<td></td>
<td>mCRPC</td>
<td>1</td>
<td>NCT03437941</td>
</tr>
<tr>
<td>TAS3681</td>
<td>monotherapy</td>
<td>mCRPC</td>
<td>1</td>
<td>NCT03437941</td>
</tr>
<tr>
<td>Selective glucocorticoid receptor antagonist</td>
<td></td>
<td>mCRPC</td>
<td>1</td>
<td>NCT03437941</td>
</tr>
<tr>
<td>CORT12581</td>
<td>+ enzalutamide</td>
<td>mCRPC</td>
<td>1/2</td>
<td>NCT03437941</td>
</tr>
</tbody>
</table>

AR, androgen receptor; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.

Metastatic Urothelial Cancer Landscape Undergoes a Transformation

An influx of FDA approvals for immunotherapeutics has rapidly expanded treatment options for patients with metastatic urothe-
lial cancer. Additionally, combination regimens and the addition of
targeted approaches, including the pan-FGFR tyrosine kinase inhib-
itor erdafitinib (Balversa), add to the progress in areas that have
been tough to crack, according to Daniel P. Petrylak, MD.

READ MORE

Scan the QR code or go to bit.ly/3dIGtB7

For a full list of references, see the article at bit.ly/32GOT5U.
NOW APPROVED

FOTIVDA®
(tivozanib) capsules

Learn more at FOTIVDAhcp.com/nowapproved
INVESTIGATORS ARE STUDYING LN-145, a novel immunotherapy developed from autologous tumor-infiltrating lymphocytes (TILs), as a potential new option for patients with unresectable or metastatic non-small-cell lung cancer (NSCLC) after disease progression on a checkpoint inhibitor and chemotherapy.

The IOV-LUN-202 trial (NCT04614103) is a phase 2 registrational study of LN-145 in patients without driver mutations. The therapy is a form of adoptive cell transfer in which TILs harvested from the patient’s tumor tissue are reinvigorated, expanded, and then infused into the patient.1,2

“This therapy is clinically relevant, and we’ve seen some people benefit from this novel immunotherapy in related clinical trials,” said Kai He, MD, PhD, a medical oncologist at The Ohio State University Comprehensive Cancer Center—The James in Columbus, as well as an assistant professor of medicine in the Thoracic Oncology Program.

“If this clinical trial is successful, this therapy would provide a relevant way to sustain response; successful development will help the patient and, we hope, convert noncurable disease to a curable one eventually.”

Although PD-1/PD-L1 immune checkpoint inhibitors (ICIs) have been incorporated into the first-line treatment paradigm as monotherapy or in combination with chemotherapy for patients with metastatic NSCLC without oncogenic mutations, most patients who receive ICIs will experience disease progression.3

The combination of pembrolizumab (Keytruda), a PD-1 inhibitor, plus chemotherapy, which is among the preferred recommendations in the National Comprehensive Cancer Network guidelines,4 is a “popular regimen,” but the majority of patients relapse within 7 to 8 months, according to Benjamin C. Creelan, MD, a medical oncologist and clinical researcher in the Department of Thoracic Oncology at Moffitt Cancer Center in Tampa, Florida.

Checkpoint inhibitors may not work in some cancers because of the lack of T cells infiltrating the tumors, Creelan explained. “This trial is taking that exact population and trying an immune therapy again for them using TILs,” Creelan said.

TIL therapy has shown signs of efficacy in metastatic NSCLC. In 2020, Creelan and colleagues presented findings from a phase 1 study (NCT03215810) in which TIL therapy resulted in an ORR of 25% in 20 patients with metastatic NSCLC who had disease progression after prior treatment with nivolumab (Opdivo).5

IOV-LUN-202 TRIAL DETAILS

In the IOV-LUN-202 trial, investigators are seeking to enroll 95 patients with unresectable or metastatic NSCLC who have progressed after a single line of treatment with ICI therapy plus chemotherapy with or without bevacizumab (Avastin) and whose tumors do not have an actionable driver mutation or translocation in genes such as EGFR, ALK, and ROS.1,2

To manufacture the TIL therapy, investigators will obtain a 1.5-cm sample of tumor tissue from each patient and send it to a manufacturing facility where the TILs will be reinvigorated and expanded. Prior to TIL infusion, patients will receive IV nonmyeloablative lymphodepletion with cyclophosphamide (60 mg/kg x 2) plus fludarabine (25 mg/m² x 3), followed by a single infusion of autologous LN-145 (day 0) and up to 6 doses of IL-2 (600,000 IU/kg).2

The IL-2 infusions are an important part of the therapy, Creelan said. “We know that the T cells that we culture still depend on those cytokines to carry out their activity when they are infused into the body,” Creelan said. “Giving patients a little extra boost afterward is believed to be important, but the amount of IL-2 and the length are up for discussion.”

The nonrandomized study will have 4 cohorts (FIGURE). Cohort 1 will enroll 40 patients whose tumors do not express ICI, immune checkpoint immunotherapy; IRC, independent review committee; NSCLC, non-small cell lung cancer; ORR, objective response rate; TIL, tumor-infiltrating lymphocyte; TPS, tumor proportion score.

Tissue obtained from core biopsy.

FIGURE. LN-145 TIL Therapy in Metastatic NSCLC1,2

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable, or metastatic NSCLC</td>
<td>Primary</td>
</tr>
<tr>
<td>Negative for driver mutations</td>
<td>• ORR per RECIST 1.1 by IRC for cohorts 1 and 2 or by investigator for cohorts 3 and 4</td>
</tr>
<tr>
<td>Radiographic disease progression</td>
<td>Select secondary</td>
</tr>
<tr>
<td>1 prior systemic therapy including ICI + chemotherapy</td>
<td>• Safety; efficacy of TILs from core biopsies (cohort 3)</td>
</tr>
</tbody>
</table>

Cohort 1
- TPS <1% prior to ICI; ≥ 1 resectable lesion (n = 40)

Cohort 2
- TPS ≥ 1% prior to ICI; ≥ 1 resectable lesion (n = 40)

Cohort 3
- TPS < 1% prior to ICI; unable to safely undergo surgical tissue procurement (n = 15)

Cohort 4
- Retreatment (previously treated with LN-145 in cohorts 1, 2 or 3)
PD-L1 prior to ICI therapy with a tumor proportion score (TPS) of less than 1%, whereas cohort 2 will enroll 40 patients with a TPS of 1% or greater before ICI therapy. Cohort 3, designed for 15 patients with a TPS of less than 1%, will use core biopsies for tumor acquisition for patients who are unable to safely undergo surgery.

Cohort 4 will comprise patients who have been previously treated with LN-145 in cohort 1, 2, or 3 and who may need retreatment with the TIL therapy.

“The vast majority of patients with stage IV lung cancer will progress, even on the state-of-the-art therapy,” He noted.

The primary end point in IOV-LUN-202 is ORR using RECIST 1.1 criteria, as assessed by the independent review committee (cohorts 1 and 2) or by the investigator (cohorts 3 and 4). Secondary end points include complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression-free survival, and OS.

Investigators are recruiting patients in 50 sites in the United States and Europe. The first site was activated in January 2021.

“This is highly sophisticated, hospital-based therapy, involving surgical and nonsurgical harvesting of the TILs, isolating the TILs, proliferating, and stimulating the cells. The patient will have lymphodepletion, the infusion of TIL, and then a short course of IL-2,” He said.

Iovance Biotherapeutics, Inc, the developer of LN-145, has optimized a manufacturing process originally pioneered by the National Cancer Institute. The company can deliver a cryopreserved TIL infusion product in 16 to 22 days.

Creeelan said Moffitt Cancer Center is manufacturing the TIL therapy for the study. Meanwhile, Iovance is constructing a manufacturing facility in Philadelphia, Pennsylvania. Construction of the clean rooms was completed in late 2020, with commercial manufacturing on track to start in 2022, the company said.

PROMISING MELANOMA RESULTS

Investigators also have been interested in pursuing TIL therapy for patients with NSCLC because of encouraging results in melanoma.

Most recently, at the American Association for Cancer Research Cancer Annual Meeting 2021, investigators presented findings from the phase 2 C-144-01 study (NCT02360579) involving a cohort of patients who were treated with a cryopreserved form of lifileucel (LN-144) that had been centrally manufactured in a 22-day process.

Cohort 2 enrolled 66 patients with unresectable or metastatic melanoma who had been treated with at least 1 prior therapy including an anti–PD-1 inhibitor and, for those with a BRAF V600 mutation, a BRAF inhibitor or a combination of BRAF plus MEK inhibition. The median age of the patients was 55 years (range, 20-79) and the mean number of prior therapies in the cohort was 3.3.

After a median study follow-up of 28.1 months, the ORR among patients in the cohort was 36.4%, with 3 patients experiencing CRs and 21 exhibiting partial responses (PRs). The DCR, which includes patients with stable disease as well as responses, was 80.3%. The median DOR was not reached (range, 2.2-35.2+ months).

The adverse event (AE) profile was consistent with the advanced disease of the participants and the safety profile of the nonmyeloablative lymphodepletion and IL-2 regimens that participants also received, investigators noted.

The incidence of treatment-emergent AEs of grade 3 or 4 severity was 97.0%, most frequently thrombocytopenia, anemia, and febrile neutropenia. Two patients died, 1 from an intra-abdominal hemorrhage possibly related to TIL therapy and the second from acute respiratory failure not associated with TILs.

The TILs used to produce lifileucel for the study were procured from tumor tissue in numerous organ sites, showing that the therapy could be manufactured successfully regardless of the site of origin.

FURTHER RESEARCH INTO LN-145

Investigators continue to study LN-145 in several other cancers. In head and neck squamous cell carcinoma (HNSCC), investigators are studying the immunotherapy in combination with pembrolizumab in patients with advanced recurrent or metastatic disease who have not been treated previously with ICIs. Interim results were presented in November 2020 at the 35th Anniversary Annual Meeting of the Society for Immunotherapy of Cancer.

In cohort 2A of the phase 2 IOV-COM-202 study (NCT03645928), the response rate was 44.4%, including 1 complete response and 3 partial responses, among 9 patients with HNSCC who received a one-time TIL administration plus pembrolizumab, for a DCR of 88.9%. Median DOR was not reached at 8.6 months of median study follow-up (range, 1.0+ to 10.9+ months).

The study is continuing to evaluate TIL therapy in 7 cohorts as monotherapy or in combination with pembrolizumab in patients with melanoma, HNSCC, or NSCLC, or in combination with nivolumab plus ipilimumab (Yervoy) in NSCLC.

The trial will test 3 types of TIL therapy: lifileucel (LN-144)/LN-145, produced on a 22-day manufacturing schedule; a third-generation version of LN-144, manufactured in 16 days; and LN-145-S1, a PD-1–selected TIL product.

Additionally, investigators are studying LN-145 as monotherapy and in combination with pembrolizumab in patients with metastatic cervical cancer in a phase 2 trial (NCT03108495).
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\textsuperscript{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 STATUS¹,²

<table>
<thead>
<tr>
<th>OVERALL POPULATION (N=733)</th>
<th>HRd POPULATION (n=373)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in the risk of progression or death</td>
<td>Reduction in the risk of progression or death</td>
</tr>
<tr>
<td><strong>38%</strong></td>
<td><strong>57%</strong></td>
</tr>
<tr>
<td>MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR, 0.62; 95% CI, 0.50-0.76) <em>P</em>&lt;0.0001</td>
<td>MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO (HR, 0.43; 95% CI, 0.31-0.59) <em>P</em>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Study Design¹²:** 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%).

- **Increased creatinine (40%), decreased magnesium (36%), increased AST (35%), and increased ALT (29%).**

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


IL = first-line; CI = confidence interval; CR = complete response; HR = hazard ratio; HRd = homologous recombination deficient; PFS = progression-free survival; PR = partial response.

Visit ZEJULAHCP.COM to explore the PRIMA data.
5.3 Hypertension and Cardiovascular Effects
Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 3 or 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range, 1 to 531 days) and with a median duration of 12 days (range, 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3 or 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range, 4 to 504 days) and with a median duration of 15 days (range, 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

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

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter, during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the dose of ZEJULA, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).

4.2 Bone Marrow Suppression
Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or pancytopenia, have been reported in patients treated with ZEJULA (see Adverse Reactions (6)). In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, 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 in 22%, 23%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

In NOVA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 1%, and 2%, respectively, of patients.

In QUADRA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 38%, 27%, and 12%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy (Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).
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 and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions 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: 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>ZEJULA (n=367)</td>
<td>Placebo (n=179)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36</td>
<td>15</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

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>ZEJULA (n=367)</td>
<td>Placebo (n=179)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
<td>15</td>
</tr>
</tbody>
</table>

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

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

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

(continued on next page)
Non-infectious Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) [see Warnings and Precautions (5.5)]

Advise patients to stop taking ZEJULA and seek medical advice immediately if they develop any of these signs or symptoms including seizure, headaches, altered mental status, or vision changes. Advise patients to contact their healthcare provider if they develop any of these signs or symptoms [see Warnings and Precautions (5.5)].

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 (5.6)] and Use in Specific Populations (8.2).

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)].

ZICLIB 03/2021
Trademarks are owned by or licensed to the GSK group of companies.

Manufactured for GlaxoSmithKline Research Triangle Park, NC 27709
©2021 GSK or licensor. NPI5903101001 March 2021
Produced in USA.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (n=463) %</th>
<th>Grades 3-4 (n=463) %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

AST/ALT = Aspartate transaminase/alanine aminotransferase. 
Common Terminology Criteria for Adverse Events version 4.02.
Anemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normochromic normocytic anemia.
Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.
Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection, and neutropenic sepsis.

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

Blood and Lymphatic System Disorders: Pancytopenia.
Immune System Disorders: Hypersensitivity (including anaphylaxis).
Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES).
Psychiatric Disorders: Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).
Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.
Skin and Subcutaneous Tissue Disorders: Photosensitivity.
Vascular Disorders: Hypertensive crisis.

6.3 Special Considerations

6.3.1 Postmarketing Experience
ZEJULA has been assessed in postmarketing adverse reactions data from approximately 16,100 patients treated with ZEJULA in the QUADRA study or NOVA study. These events are tabulated below, ordered by body system and characterized using MedDRA 10.1 terminology at the preferred term level.

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

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

[total bilirubin ≤1.5 x upper limit of normal (ULN) to 3.0 x ULN and any aspartate transaminase (AST) level]. Monitor patients for hematologic toxicity and reduce the dose further, if needed [see Dosage and Administration (2.3) of full prescribing information].
For patients with mild hepatic impairment (total bilirubin ≤1.5 x ULN and any AST level or bilirubin ≤1 x ULN and AST >1 ULN), no dose adjustment is needed.
The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST level) [see Clinical Pharmacology (12.3) of full prescribing information].

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

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

Contraception
Females: Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months following the last dose.

Infertility
Males: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) of full prescribing information].

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

8.5 Geriatric Use
In QUADRA, 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 sensitivity 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 [total bilirubin ≤1.5 x upper limit of normal (ULN) to 3.0 x ULN and any aspartate transaminase (AST) level]. Monitor patients for hematologic toxicity and reduce the dose further, if needed [see Dosage and Administration (2.3) of full prescribing information].
Clinical Perspectives

BREAST CANCER

Surgical Options for Lymphedema Emerge

by KYLE DOHERTY

PROMISING TECHNIQUES IN surgical oncology are on the horizon for the treatment of lymphedema, according to Susan B. Kesmodel, MD.

“Anything that we can do as surgeons to primarily reduce lymphedema would be helpful for patients,” said Kesmodel, associate professor, director of Breast Surgical Oncology, and coleader of Breast Site Disease G at the Sylvester Comprehensive Cancer Center at the University of Miami Health System in Florida. “For patients who do develop lymphedema, if we can offer them both surgical and nonsurgical interventions, we can have a significant impact not only on their quality of life but [we] also could potentially reduce health care costs because the management of lymphedema can be very costly.”

In the past, lymphedema has primarily been treated with debulking procedures that remove the excess fluid through liposuction. These types of procedures typically provide only temporary improvement and do not address the condition physiologically. However, in recent years more physiologically impactful methods and considerations have been developed to curb the incidence and severity of lymphedema in patients with breast cancer.1

THE SURGICAL PERSPECTIVE

Patients who undergo axillary lymph node dissection are at an increased risk for developing lymphedema. Kesmodel said that reducing the extent and instance of axillary surgery, as long as it is oncologically safe, can have a major effect on lymphedema rates in patients with breast cancer.

“The extent of axillary surgery has a significant impact on the development of lymphedema,” Kesmodel explained. “It’s more common in those patients who undergo axillary lymph node dissection; most of the studies have demonstrated that the risk in that patient group is around 20%. With the addition of radiation therapy, this number can increase to as high as 30% to 35%.”

The use of axillary surgery has been reduced in recent years using procedures such as sentinel lymph node biopsy (SLNB). Results from an evaluation of 125 patients who underwent SLNB or axillary lymph node dissection for the staging of breast cancer showed that SLNB had a significant effect in preventing lymphedema. Specifically, lymphedema was observed in 2 of 77 patients (2.6%) who underwent SLNB compared with 13 of 48 patients (27%) who had an axillary lymph node dissection.2 Additionally, a systemic review of data from randomized controlled trials, which examined 5161 patients who had SLNB, small numbers of adverse events were reported following the procedure including lymphedema (range, 0%-11%), pain (11%-16%), sensory disorders (2%-22%), and motor disorders (0%-9%) at 6 months after surgery.3

NEW TECHNIQUES REDUCE ADVERSE OUTCOMES

Axillary reverse mapping is another technique that may reduce the extent of lymphedema in patients who undergo axillary surgery. The minimally invasive technique uses dye injection to distinguish and conserve upper-limb lymphatics during axillary surgery. In a randomized, controlled trial of 48 patients who had axillary lymph node dissection, 24 patients in the study group underwent using axillary reverse mapping, and 24 patients in the control group underwent a conventional axillary lymph node dissection. At the 6-month follow-up, lymph node visualization was achieved in 20 patients (83.3%) in the study group. The incidence of lymphedema was 16.7% in the control group compared with 4.2% in the experimental group.4

Kesmodel said another option for managing lymphedema is lymphaticovenular anastomosis, also known as lymphovenous bypass. During this surgical procedure, a recipient vein is identified cutaneously and aided by lymphangiography, an anastomosis is created using microsurgical techniques. Several approaches can be utilized to perform the anastomosis, all requiring a microscope with high-magnification optics (TABLE4-7). The procedure requires time, meticulous technique, and experience.1

In a prospective evaluation of 100 patients with extremity lymphedema secondary to cancer treatment who underwent lymphovenous bypass, investigators observed...
symptom improvement in 96% of patients. A reduction in limb volume was seen in 74% of patients, with an average volume reduction of 42% at 12 months.²

Findings from another single-center prospective study of 100 patients with upper and lower extremity lymphedema showed that, after a mean follow-up of 25 months, decrease in upper and lower limb circumference was observed in 52.1% of patients with a mean decrease of 6%. Patients in this study also completed a quality-of-life assessment using the Lymphoedema Functioning, Disability, and Health Questionnaire (Lymph-ICF). Mean Lymph-ICF score significantly decreased from a preoperative 43.9 to 30.6 postoperative, representing a significant improvement in patient-reported quality of life.³

Of note, lymphaticovenular anastomosis comes with its own set of challenges. The procedure requires microvascular expertise and access to the necessary equipment, Kesmodel explained. There is also a concern for bleeding-related complications, although these have rarely been observed. In addition, allergic reactions may occur due to the use of isosulfan blue (Lymphazurin).

“If a more simplified lymphatic anastomosis approach is found to be effective, that is something that could potentially be used by a surgeon in any practice who doesn’t have access to advanced surgical techniques,” Kesmodel said. “A procedure like that could be more widely accepted and implemented across the United States and in countries around the world.”

Vascularized lymph node transplant (VLNT) to improve physiologic lymph clearance is a relatively new technique that presents another option for patients with lymphedema. Lymph nodes are harvested from a donor site with their supporting artery and vein and are then transferred to the recipient site of the affected area. Transplant nodes can be harvested from the groin, axilla, supraclavicular, submental, thoracic, and omental flaps.⁷

VLNT carries the risk of donor site morbidity. Surgeons also must consider the possibility of iatrogenic lymphedema and the location of the scar. “Lymphedema has been a problem for a long time,” Kesmodel concluded. “It is less of a problem now because we’ve reduced axillary surgery, among other things, but I still believe it’s a significant quality-of-life issue for patients and we really need to do our best to minimize it.”

---

Novel Combo Shows Early Efficacy in Ovarian Cancer

**by KRISTI ROSA**

**TISLELIZUMAB, A NOVEL PD-1 INHIBITOR,** is demonstrating early signs of efficacy in combination with sitravatinib, an investigational tyrosine kinase inhibitor (TKI), in patients with recurrent platinum-resistant epithelial ovarian cancer, according to Jeffrey C. Goh, MBBS, FRACP.

The doublet resulted in an objective response rate (ORR) of 26% (95% CI, 15.3%-40.3%), among 53 efficacy-evaluable patients from cohort E of the phase 1b BGB-900-103 trial (NCT03666143), Goh said in a presentation during the American Association for Cancer Research Annual Meeting 2021.

All responses were partial (n = 14). Fifty-one percent of patients had stable disease (n = 27), and 17% had progressive disease (n = 9). The median duration of response was 4.7 months (95% CI, 2.83–not evaluable), and the disease control rate was 77% (95% CI, 63.8%-87.7%).

Per investigator assessment, the median progression-free survival (PFS) was 4.1 months (95% CI, 4.0–22.8) at a median follow-up of 6.9 months, and the median overall survival (OS) was 12.9 months (95% CI, 6.2–17.0) at a median follow-up of 7.5 months.

“Tislelizumab in combination with sitravatinib was generally well tolerated and had a manageable safety/tolerability profile in patients with anti–PD-1/PD-L1 antibody-naïve recurrent platinum-resistant ovarian cancer,” said Goh, a medical oncologist at Icon Cancer Centre in Brisbane, Australia. “The results from this phase 1b study support tislelizumab in combination with sitravatinib as a potential treatment option for patients with platinum-resistant ovarian cancer and further investigation is warranted.”

The frontline standard of care for patients with ovarian cancer is platinum-based chemotherapy with or without bevazucizumab (Avastin). However, disease recurrence is frequent and almost all patients will become refractory or develop resistance to platinum-based treatment, according to Goh. No immune checkpoint inhibitors have been approved for patients with the malignancy, he noted.

**BEYOND ANTI–PD-1 MONOTHERAPY**

Findings from several early phase 1/2 trials have demonstrated the limited effectiveness of PD-1/PD-L1 immune checkpoint inhibitors when used as single agents in heavily pretreated patients with ovarian cancer. The estimated ORRs in these patients ranged from 10% to 15%, Goh said.

Tislelizumab, a humanized, anti-PD-1 monoclonal antibody, is designed to minimize binding to Fcγ receptor on macrophages to abrogate antibody-dependent phagocytosis, which can overcome the attack of normal lymphocytes by immune cells.

Sitravatinib is an oral spectrumspecific TKI designed to target TAM receptors and split family receptor kinases in VEGFR/KIT. Inhibition of these receptors serves to reduce the number of myeloid-derived suppressor cells and regulatory T cells and increase the ratio of M1/M2 polarized macrophages; this could overcome an immunosuppressive tumor microenvironment and enhance antitumor responses.

For the phase 1b trial, investigators hypothesized that the combination of a PD-1 inhibitor and a TKI with immunomodulatory
Introducing Navista™ TS

AI-enabled, integrated tech solutions for value-based care

Value-based payment models have placed community oncology practices under more pressure than ever to manage costs while continuing to deliver high-quality care. Now there’s a new way to navigate value-based care decisions. Navista™ TS (Tech Solutions) is the only fully integrated resource for oncology practices to balance clinical and financial decision-making with connected tools and data-driven insights.

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

© 2021 Cardinal Health. All Rights Reserved. CARDINAL HEALTH, the Cardinal Health LOGO, ESSENTIAL TO CARE and NAVISTA are trademarks of Cardinal Health and may be registered in the US and/or in other countries. Patent cardinalhealth.com/patents. Lit. No. 1SS21-1396015 (05/2021)
and antitumor components could result in enhanced antitumor activity.

The trial has 8 cohorts recruiting patients with non-small cell lung cancer, renal cell carcinoma, or melanoma.

At the meeting, Goh shared data regarding the use of the combination in cohort E, which was composed of patients with recurrent platinum-resistant ovarian cancer who were naïve to PD-1/PD-L1 inhibitors. Platinum resistance was defined as disease progression less than 6 months after the last platinum treatment.

To be eligible for enrollment, patients had to be 18 years or older, have histologically or cytologically confirmed advanced or metastatic unresectable solid tumors, an ECOG performance status of 0 or 1, and acceptable organ function. For cohort E, specifically, patients could not have platinum-refractory disease, nor could they have previously been exposed to a PD-1/PD-L1 agent.

Participants received intravenous tislelizumab at a dose of 200 mg every 3 weeks plus oral sitravatinib at a once-daily dose of 120 mg. Treatment was given until either disease progression, intolerable toxicity, death, withdrawn consent, or study termination.

The primary end point was safety and tolerability, and antitumor activity was the secondary end point. Potential biomarkers were included in the exploratory analyses.

As of the data cutoff of October 13, 2020, 60 patients were enrolled to cohort E; and 13 remained on the doublet. The median duration of follow-up was 6.0 months (range, 0.2-23.4).

The median age was 64 years (range, 26-80), the majority (80%) were White, and 57% had an ECOG performance status of 1. Seventy-three percent of the primary tumors were located in the ovary, 12% in the fallopian tube, 8% in the peritoneum, and 7% in another area. The majority (95%) of patients had serous histology; the rest had either mucinous (2%), endometrioid (2%), or clear cell (2%) disease (FIGURE).

The median number of previous regimens was 4 (range, 1-11). The type of previous systemic therapy was metastatic in 83% of patients, adjuvant in 67%, neoadjuvant in 35%, locally advanced in 18%, and metastatic and locally advanced in 10%. Thirty-five percent of patients previously received bevacizumab.

FIGURE. Patient Characteristics in Ovarian Cancer Trial*

<table>
<thead>
<tr>
<th>Primary tumor location</th>
<th>N = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>12%</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>8%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>73%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epithelial type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
</tr>
<tr>
<td>Mucinous</td>
</tr>
<tr>
<td>Endometrioid</td>
</tr>
<tr>
<td>Clear cell</td>
</tr>
</tbody>
</table>

*Numbers have been rounded.

Goh explained. The IP-10 level, which is involved in trafficking immune cells to inflammatory sites and mediating tumor regression, was also found to increase following treatment with the doublet.

“However, both biomarkers did not show any association with clinical response,” Goh said. Ninety-seven percent of patients experienced at least 1 treatment-emergent adverse effect (TEAE) with tislelizumab/sitravatinib, and 68% reported an effect that was grade 3 or higher in severity.

Additionally, 4 patients experienced a TEAE that resulted in death; these included 2 cases of dyspnea, 1 of respiratory failure, and 1 of malignant gastrointestinal obstruction, according to Goh. However, none of these TEAEs was determined to be related to study treatment.

Fifteen percent of patients experienced a TEAE that resulted in discontinuation of tislelizumab, 12% of which were related to the drug, whereas 23% reported a toxicity that led to sitravatinib discontinuation, 20% of which were treatment related.

The most frequently reported any-grade AE with the doublet was diarrhea (67%), followed by nausea (57%), fatigue (48%), and hypertension (40%). The most commonly reported grade 3 or higher AEs were hypertension and abdominal pain. These toxicities occurred in 18% and 12% of patients, respectively.

For a full list of references, see the article at OneLive.com.
TAZVERIK® (tazemetostat) is indicated for the treatment of:

- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

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 a confirmatory trial(s).

Efficacy results*:

- FL patients (N=95) responded to single-agent TAZVERIK in both cohorts1,2
  - 69% ORR (n=5/42) in patients with mutant-type (MT) EZH2 (n=29/42; 95% CI: 53%–82%)
  - 34% ORR (n=16/53) in patients with wild-type (WT) EZH2 (n=18/53; 95% CI: 22%–48%)

- Sustained response demonstrated in patients with both MT and WT EZH21,2
  - 10.9 months median DOR (range: 0.0+ to 22.1+) in patients with MT EZH2 (n=29/42; 95% CI: 7.2–NE)
  - 13.0 months median DOR (range: 1.0 to 22.5+) in patients with WT EZH2 (n=18/53; 95% CI: 5.6–NE)

The data for the MT EZH2 cohort were not yet mature at the time of assessment.

*TAZVERIK was studied in an open-label, single-arm, multicenter, phase 2 trial with 6 cohorts of patients, including 2 cohorts with histologically-confirmed R/R FL. Patients received 800 mg of TAZVERIK orally twice daily until confirmed disease progression or unacceptable toxicity. The major efficacy outcome measures were ORR and DOR according to the IWG-NHL criteria as assessed by independent review committees.1,2

Important Safety Information

Warnings and Precautions

- Secondary Malignancies
  The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

- Embryo-Fetal Toxicity
  Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

Important Safety Information continued on back page of this insert.
Please see Brief Summary of the Prescribing Information on the adjacent pages.
TAZVERIK (tazemetostat) tablets 200mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE
- TAZVERIK® (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

- TAZVERIK® is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSEAGE AND ADMINISTRATION

Patient Selection - Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens [see Clinical Studies]. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily for patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. This dosage is based on results from 2 dose escalation studies in which TAZVERIK 200 mg twice daily, 400 mg twice daily, 600 mg twice daily, and 800 mg twice daily were evaluated. The most common adverse reactions occurring in ≥2% of patients treated with TAZVERIK were neutropenia, thrombocytopenia, and anemia.

- For first occurrence, resume at same dose.
- For second and third occurrence, resume at reduced dose.
- Permanently discontinue after fourth occurrence.

- If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Dosage Modifications for Drug Interactions - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td>Withhold until neutrophil count is greater than or equal to 1 x 10^9/L or baseline. For first occurrence, resume at same dose. For second and third occurrence, resume at reduced dose. Permanently discontinue after fourth occurrence.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>Withhold until platelet count is greater than or equal to 50 x 10^9/L or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td>Other adverse reactions</td>
<td>Grade 3</td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first occurrence, resume at reduced dose. Permanently discontinue after second occurrence.</td>
</tr>
</tbody>
</table>

Dosage Modifications for Drug Interactions - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

<table>
<thead>
<tr>
<th>Current Dosage</th>
<th>Adjusted Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg orally twice daily</td>
<td>400 mg orally twice daily</td>
</tr>
<tr>
<td>600 mg orally twice daily</td>
<td>400 mg for first dose and 200 mg for second dose</td>
</tr>
<tr>
<td>400 mg orally twice daily</td>
<td>200 mg orally twice daily</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS

Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK, 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC_{o-τ}] at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions].

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in two cohorts (Cohorts 4 and 5) of Study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 67 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. The median number of prior therapies was 3 (range 1 to 11). Patients were required have a creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in ≥2% of patients was second primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in ≥2% of patients were thrombocytopenia and fatigue. Dose reduction due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions (≥20%) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory and mediastinal system</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6 continues on the next page.
**Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101 (continued)**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>53</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

**DRUG INTERACTIONS**

**Effect of Other Drugs on TAZVERIK** - Strong and Moderate CYP3A Inhibitors: Co-administration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations (see Clinical Pharmacology), which may increase the frequency or severity of adverse reactions. Avoid co-administration of strong or moderate CYP3A inhibitors with TAZVERIK. If co-administration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose (see Doseage and Administration). Strong and Moderate CYP3A Inducers: Co-administration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations (see Clinical Pharmacology), which may decrease the efficacy of TAZVERIK. Avoid co-administration of moderate and strong CYP3A inducers with TAZVERIK.

**Effect of TAZVERIK on Other Drugs** - CYP3A Substrates: Co-administration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates (see Use in Specific Populations, Clinical Pharmacology).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy - Risk Summary** Based on findings from animal studies and its mechanism of action (see Clinical Pharmacology), TAZVERIK can cause fetal harm if administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure at 800 mg twice daily dose (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.2 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose), At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate loss.

**Lactation - Risk Summary** There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

**Females and Males of Reproductive Potential - Pregnancy Testing** Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK (see Use in Specific Populations). Risk Summary: TAZVERIK can cause fetal harm when administered to pregnant women (see Use in Specific Populations, Pregnancy). Females - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for at least 3 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective (see Drug Interactions). Males - Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

**Pediatric Use** - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

**Juvenile Animal Toxicity Data** - In a 13-week juvenile rat toxicity study, animals were dosed daily from postnatal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:

- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Distorted testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

**Geriatric Use** - Clinical studies of TAZVERIK did not include sufficient numbers of patients with relapsed or refractory follicular lymphoma aged 65 and over to determine whether they respond differently from younger subjects.

**Renal Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease (see Clinical Pharmacology).

**Hepatic Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN]) or AST > ULN. TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment (see Clinical Pharmacology).

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility** - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and in T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Reproductive studies did not result in any notable effects in the adult male and female reproductive organs (see Use in Specific Populations).

**PATIENT COUNSELING INFORMATION** - Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Secondary Malignancies** - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they develop a second neoplasm, easy bruising, fever, bone pain, or jaundice (see Warnings and Precautions).

**Embryo-Fetal Toxicity** - Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy (see Use in Specific Populations). Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose (see Use in Specific Populations). Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose (see Use in Specific Populations, Nonclinical Toxicology).

**Lactation** - Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose (see Use in Special Populations).

**Drug Interactions** - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit, and grapefruit juice while taking TAZVERIK (see Drug Interactions).

© 2020 Epizyme®, Inc. All Rights Reserved.
Important Safety Information (continued)

- Embryo-Fetal Toxicity (continued)
  Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC0-48h]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions
In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions
Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.
Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.
Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation
Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Before prescribing TAZVERIK, please read the Brief Summary of the Prescribing Information on the adjacent pages.

References: 1. TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July 2020. 2. Data on file. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.4.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 17, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

© 2020 Epizyme, Inc. All Rights Reserved. 400 Technology Square, 4th Floor, Cambridge, MA 02139 epizyme.com TZ-FL-BR-20-0189
CETIRIZINE (QUZYTTIR), A SECOND-GENERATION intravenous (IV) antihistamine, showed comparable efficacy to IV diphenhydramine for the prevention of infusion reactions (IRs) in patients with cancer who were undergoing treatment with an anti-CD20 antibody or paclitaxel, according to results from a prospective, phase 2 trial (NCT04189588) that were presented during the 38th Annual Miami Breast Cancer Conference®.

Findings showed that the IR rate in patients who received IV cetirizine was 11.8% (2 of 17 patients) compared with 17.6% (3 of 17) in those who received IV diphenhydramine. Overall, the study comprised 25 patients who received anti-CD20 therapy for lymphoma, leukemia, or immune disorders and 9 patients with solid tumors, including breast, lung, cervical, and bladder cancers. Of 3 patients with breast cancer who received cetirizine, 1 experienced an IR.

“This was the first prospective, randomized, controlled trial evaluating IV antihistamine pretreatment for the prevention of IRs,” Jarrod P. Holmes, MD, FACP, a medical oncologist at St Joseph Health Cancer Center in Santa Rosa, California, and coinvestigators noted in the poster presented at the meeting. “IV cetirizine was associated with less sedation, less time in the treatment center, and fewer treatment-related AEs [adverse effects] than IV diphenhydramine.”

Pretreatment with antihistamine for drug-induced hypersensitivity is recommended for use with chemotherapies, including paclitaxel, for patients with breast cancer. IV cetirizine has been shown to treat patients with acute urticaria with outcomes comparable to those of IV diphenhydramine but with fewer toxicities. The study authors suggested that IV cetirizine may also show promise as a pretreatment of IRs.

In the prospective, double-blind, randomized, controlled, phase 2 trial, investigators sought to compare the incidence of IRs with treatment with an anti-CD20 antibody such as rituximab (Rituxan) or obinutuzumab (Gazyva), or with paclitaxel, following pretreatment with IV cetirizine (n = 17) or IV diphenhydramine (n = 17) during infusion. IRs were defined as flushing, itching, alterations in heart rate and blood pressure, dyspnea, chest discomfort, acute back or abdominal pain, fever, shaking, chills, nausea, vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, syncope, or dizziness.

Pretreatment was given with a single IV dose of 10-mg cetirizine or IV diphenhydramine at 50 mg in 34 patients who were being treated with paclitaxel, rituximab, a rituximab biosimilar, or obinutuzumab at the first cycle or retreatment after 6 months or in patients with persistent IRs while on maintenance or retreatment. To be eligible for enrollment, patients had to be 18 years or older, could be male or female, and required treatment premedication with an antihistamine for hypersensitivity IRs linked with anti-CD20 therapy or paclitaxel. Patients were excluded if they had a high risk of developing tumor lysis syndrome, may have had contraindications with an antihistamine, had received any antihistamine within 24 hours prior to receiving the study drug regardless of the administration route, and had received an H₂ antagonist in the prior 4 hours before receiving study drug, were excluded.

Investigators noted that the primary end point of the trial was the incidence of IRs following pretreatment. The key secondary end point was sedation score due to IV antihistamines. Sedation was assessed by health care providers and patients on a scale of 0 to 4 (0 = none; 4 = extremely severe/asleep). Time to readiness for discharge served as another efficacy end point.

The patient population comprised those with both hematologic and solid tumors enrolled between March 25, 2020, and November 23, 2020. The median age of the participants was 66.0 years (range, 36-87), 35.3% were female, and most were White (76.5%) and not Hispanic or Latino (82.4%).

Additional data showed that the mean patient-related sedation scores in the IV cetirizine arm were 0.5 (SD, 0.72), 0.6 (0.61), and 0.1 (0.33) vs 1.3 (1.26), 0.9 (1.14), and 0.4 (0.71) in the IV diphenhydramine arm at 1 hour, 2 hours, and at discharge, respectively, as rated by the patients enrolled in the trial. These data were similar to the health care provider-rated sedation scores.

The median time for discharge readiness was 24 minutes shorter with IV cetirizine compared with IV diphenhydramine, at 4 hours and 18 minutes and 4 hours and 42 minutes, respectively.

Regarding safety, fewer patients experienced treatment-related AEs (TRAEs) with IV cetirizine (n = 2) than with IV diphenhydramine (n = 4). Treatment-emergent AEs (TEAEs) occurred in 8 and 9 patients, respectively. In the IV cetirizine arm, these TEAEs were mild in 2 patients, moderate in 4, severe in 1, and life-threatening in 1; none were fatal. In the IV diphenhydramine arm, 3 cases were mild, 5 were moderate, and 1 was fatal; no severe or life-threatening TEAEs were reported. There were 0 AEs that led to discontinuation in either arm.

The TRAEs in the IV cetirizine arm included insomnia, dyspepsia, and malaise. In the IV diphenhydramine arm, TRAEs were diarrhea, injection site pain, headache, somnolence, dizziness, and lightheadedness.

In the poster, investigators noted that study limitations include the small sample size without formal statistics. “However, the results of key secondary end points of sedation score, time to discharge, and safety profile are consistent with the results from the studies with IV cetirizine in acute urticaria,” the authors stated.

REFERENCE

IV Cetirizine Prevents Infusion Reactions
by GINA MAURO
IN THE UNITED STATES, a geographic mismatch exists between the number of medical oncology and radiation providers and patients needing care, with more specialists clustered in urban and metropolitan areas. This imbalance happens, investigators said, because of the infrastructure needed to support high-quality oncology care. Larger geographic areas offer access to hospitals and universities, clinical trials, peers, and centers that furnish radiation services.

Addressing the gap in providers in rural areas is important because it affects patient care, experts say. Cancer incidence rates and deaths are higher in rural areas than in metropolitan areas. One analysis published in 2017 looked at 5-year cancer incidence and mortality rates between 2009 and 2013. Investigators found that in metropolitan counties, cancer incidence was 447 cases per 100,000 people (range, 446-456 depending on county characteristics), whereas in rural counties, the incidence was 460 per 100,000 (range, 439-477).

Mortality rates were 166 per 100,000 in metropolitan counties (range, 164-173) and 182 per 100,000 in rural counties (range, 174-185). The difference was statistically significant for both benchmarks ($P < .001$).

“Access to oncology services is impacted by the low density of oncologists in the rural settings,” Smita Bhatia, MD, MPH, director of the Institute for Cancer Outcomes and Survivorship at the University of Alabama at Birmingham (UAB) School of Medicine, said in an interview with OncologyLive®. She is also vice chair for outcomes in the Department of Pediatrics and associate director for outcomes research of the UAB Comprehensive Cancer Center, and associate director of the Center for Outcomes and Effectiveness Research and Education.

“We know that if patients with cancer who are undergoing treatment aren’t carefully monitored, they may have [adverse] effects or an exacerbation of symptoms, or other things that could go wrong. Then when the situation really deteriorates, they may go to emergency departments,” Susan Dentzer, senior policy fellow for Robert J. Margolis Center for Health Policy at Duke University in Durham, North Carolina, said in an interview.

GEOGRAPHIC IMBALANCE

In 2019, 64% of US counties had no oncology care providers whose primary practice site was within that county, and 12% had no oncologists in the adjacent counties, according to a recent analysis in JCO Oncology Practice. Two investigators in this study looked at the geographic distribution of oncologists and oncology pharmacists registered in the 2019 National Provider Identifier database and found wide discrepancies in the number of oncologists across geographic regions.

More than 65% of oncologists were based in 4 of 9 US Census Bureau divisions; areas with the fewest oncologists were located in the West North Central and West South Central divisions (Figure 1). Of note, a lower availability of cancer care providers was negatively associated with higher cancer rates (correlation, -0.085; $P < .01$).

Another analysis conducted by the American Society of Clinical Oncology (ASCO) showed that just 403 of the 1698 US hematology and medical oncology practices listed in the CMS Physician Compare database have sites in rural areas. Almost 9 in 10 radiation oncologists work in urban or suburban communities (47% and 41%, respectively). The proportion of those practicing in rural areas declined from 16% in 2012 to 13% in 2017, according to the American Society for Radiation Oncology (ASTRO).
Meanwhile, the percentage of the US population living in rural areas varies from 15% to 19%, depending on the definition used. The US Census Bureau, for example, doesn’t actually define “rural.” It classifies Urbanized Areas as those with 50,000 or more people and Urban Clusters as those with 2,500 to fewer than 50,000 people.

In the 2010 Census, 59.5 million people, 19.3% of the population, were considered to be living in rural areas, and more than 95% of US land area is still classified as rural.²

The Office of Management and Budget (OMB) considers all areas outside of a metropolitan statistical area as rural. In 2010, non-metropolitan counties contained 46.2 million people, approximately 15% of the total population and covered 72% of the land area of the country.

The Federal Office of Rural Health Policy uses the OMB classification but uses an additional measure that attempts to allow for better identification of rural areas. By this measure, 57 million people, approximately 18% of the population, and 84% of the nation’s land area are considered rural.

**TACKLING GAPS IN CARE**

ASCO and ASTRO have implemented initiatives to focus on oncology care in rural areas. In 2019, both organizations launched efforts to address the needs of oncology care providers in rural areas and better support oncologists regarding provider education and training, telehealth, and research³ (FIGURE 2).

Bhatia, who is on ASCO’s cancer care task force, said the organization has developed recommendations for addressing oncology care and supporting rural oncologists; these are in manuscript form and will be published soon. One recommendation, she said, is to increase education, training, and mentoring opportunities for those practicing in rural areas, as well as develop the workforce development and build capacity.

Continuing education for physicians and staff has always been an issue in rural areas, said David Beyer, MD, medical director of radiation oncology at Cancer Centers of Northern Arizona Healthcare in Sedona. “The COVID-19 pandemic has forced us to experiment. A lot of CME [continuing medical education] last year was virtual, and it may be that we discovered quite by accident the models that might work in the future.”

The ASCO task force also recommended the following: harnessing the growing quality improvement and practice health programs to improve cancer care delivery in rural settings; collecting and analyzing additional data to better understand the current state, needs, and challenges of the rural cancer care workforce in both oncology and nononcology; and promoting research of the design and implementation of cancer care delivery models in the rural setting, Bhatia said in an interview.

Building up the oncology workforce in rural areas will require making changes to training programs, said Geraldine M. Jacobson, MD, MPH, MBA, FACR, FASTRO, a radiation oncologist, professor and chair of the Department of Radiation Oncology at West Virginia University Cancer School of Medicine in Morgantown, West Virginia.

One way to do this would be to invest in a national program that supports physicians who want to practice in rural communities. “We need to get people from rural areas into our medical pipeline who will practice in rural areas and that includes maintaining our smaller training programs,” she said in an interview. “Money follows money and technology follows technology. If we want a different outcome, we have to do something different.”

**A DIFFERENT MODEL IS NEEDED**

Capacity building and increasing the density of oncology providers and ancillary support staff is important, but that won’t entirely address the rural care issues, Dentzer said.

A different model of care for patients is needed, where they are supported in their homes with telehealth services from clinicians and visits from advanced practice providers. Even in less populous states such as New Mexico, oncologists generally practice in urban or suburban areas, and it’s unlikely they will move to outlying areas, she noted.

---

**FIGURE 2. ASCO’s Plan to Support Oncology Providers in Rural Areas⁴**

- **Provider education:** Equip all members of the cancer care team with training and support
- **Workforce:** Improve understanding of the unique needs of the rural care workforce.
- **Research:** Develop research to better understand the magnitude of differences in outcomes in rural and nonrural settings.

---

**FIGURE 1. Percentage of US Counties With No Oncologists by Census Division²**

There is a wide geographic variation in the availability of oncologists in the United States, according to an analysis of primary practice locations by county and census tracts.
The business model for them [to operate in rural areas] would be unsustainable for the most part. It’s just not going to happen. We focus too much on getting patients and specialists in the same room. The question becomes how to get patients and specialists’ knowledge in the same room. And we’ve found we can put people together via technologies and via telehealth. It’s not about people transfer; it’s about knowledge transfer.”

Dentzer pointed to Project ECHO, the now-global effort that originated at the University of New Mexico School of Medicine as an example.

Project ECHO—which stands for Extension for Community Healthcare Outcomes—began in 2003 as a model to help specialists at the University of New Mexico in Albuquerque support primary care doctors and other clinicians in outlying areas of the state in treating treat patients with hepatitis C. Project ECHO has since grown to include global initiatives in many disease areas, including HIV, tuberculosis, rheumatology, maternal health, and opioid use disorders, as well as oncology.7

Oncology organizations are beginning to launch similar efforts. One is ASTRO’s Peer-to-Peer Match, which was released in June 2020. The online platform facilitates relationships and connects ASTRO members for peer review of patient cases. It allows clinicians to search for those with similar expertise to assist in evaluating treatment plans.8

Peer-to-Peer Match helps to address a challenge radiation professionals in rural areas face, Beyer said. “This program is essentially a ‘Match.com’ for radiation oncologists in rural settings who want to review plans with somebody else, someone who has a similar practice style, a similar practice size, similar technical capabilities.”

Rural oncology patients can also be served by “hospital-at-home” programs, Dentzer said. An example of one such program is Huntsman at Home offered by Huntsman Cancer Institute at the University of Utah in Salt Lake City.

The institute launched Huntsman at Home in 2018 to support patients and caregivers and manage acute and post-surgical care, as well as end-of-life care. It uses nurse practitioners and registered nurses, working with oncology teams, to deliver acute level care at home.9

An evaluation of the program’s utilization outcomes was presented at the 2020 ASCO Virtual Scientific Program. Investigators found evidence that the Huntsman at Home program can improve value by reducing hospitalizations, emergency department visits, and costs. Investigators focused on patients at hospital discharge who needed continued acute level care. They found that for the first 14 months of the program, 19.5% of patients in Huntsman at Home (n = 169) had 1 or more unplanned hospitalizations compared with 35.4% of patients in a similar group outside the 20-mile radius of the hospitals (n = 198).10

Additionally, 14.2% of Huntsman at Home patients had 1 or more emergency department visits vs 23.2% for the comparison group. Mean costs were also lower in the Huntsman at Home group ($10,238) vs the usual care group ($21,363).

“This was an initial test of the concept in oncology, and it shows that extending acute level cancer care into the home and communities of cancer patients utilizing a hospital-at-home model can significantly improve patient experience and outcomes,” said Kathi Mooney, PhD, RN, who presented the results. Mooney is a distinguished professor at the University of Utah College of Nursing and coleader of the Cancer Control and Population Sciences Program at the Huntsman Cancer Institute.

Currently, the program is available to patients within a 20-mile radius of the hospital in Salt Lake City. Hospital administrators are also working to increase Huntsman at Home’s reach, extending care to several rural counties in the state. In July 2020, Huntsman Cancer Institute received a $4.5 million gift from the Huntsman family to expand the program to rural Utah.11

The institute is in the planning process for expanding the program to Carbon, Grand, and Emery counties, working with the communities identified for the rural expansion and the Huntsman Cancer Institute clinical teams, according to a Huntsman spokesperson. These counties were selected following evaluation of Utah’s cancer burden and conversations with community organizations and elected officials in these areas. ■

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

Review Your Finances Now to Stay on Track in 2021
by Ken Nuss

IT’S ALWAYS A GOOD TIME to do a financial review to make sure your savings and investments are aligned with your goals.

► Review individual retirement accounts, 401(k), and other plan contributions.

If you didn’t fully fund your retirement plan(s) in 2020, you should consider what you can afford to salt away this year. Contributions to 401(k) plans reduce your taxable wages. Many employers will let you make an additional one-time contribution up to the IRS limit.

► Review your asset allocation and rebalance if needed.

Confounding expectations, the stock market has boomed in the past year. As a result, you may find that your asset allocation is unbalanced. If you do need to rebalance your taxable investments, be aware of tax strategy. For instance, if you have unrealized losses, you can sell off losing investments to offset gains from selling your winners.

► Consider all your options. You may be able to get a better rate than you expect.

Known as a multiyear guarantee annuity or a CD-type annuity, a fixed-rate annuity behaves a lot like a bank certificate of deposit, with some notable differences. Like a CD, it pays a guaranteed interest rate for a set period, usually 3 to 10 years. Unlike a CD, the interest credited to the annuity is tax-deferred until you withdraw it.

► Keep beneficiaries updated.

Check to make sure the listed beneficiaries on annuities, life insurance policies, and retirement plans are up to date. Life changes such as marriage, divorce, the birth of children or grandchildren or the death of a loved one may require you to update your beneficiaries. ■

Ken Nuss is the founder and CEO of Annuity Advantage, a leading online provider of fixed-rate, fixed-indexed and immediate income annuities.
CONNECT WITH PURPOSE
TECENTRIQ is committed to helping you treat patients

Learn more about our FDA-approved indications at TECENTRIQ.com/info
Evolving Psychosocial Care Models Step Forward as the Next Targeted Cancer Therapy

by ALYSON B. MOADEL-ROBBLEE, PhD

WHEN I WAS TEENAGER, I witnessed my mother struggle with breast cancer and the toll her treatment had on her physical and emotional well-being. I was also a casualty of that war and still bear many scars decades after her death. The one saving grace we both had during those harrowing years was my mother’s drive to find a support system comprising other people facing cancer. During this search, my mother also investigated complementary therapies that peers had used to help cope with their fears, adverse effects, and feelings of helplessness.

At the time, many of these complementary therapies were not embraced by the medical community. In addition to the challenge of trying to locate and access these therapies, my mother had to learn through trial and error which modalities worked best for her and when. For example, although she derived important benefits from deep massage and yoga during earlier stages of disease, she turned less often to physical interventions such as visual imagery and art therapy as her cancer progressed.

Just as genetic testing and targeted therapies have enabled cancer providers to determine the best treatments for an individual’s tumor, my mother’s experience has taught me that psychosocial care needs to go beyond a “one-size-fits-all” approach and be tailored to each person.

TARGETED PSYCHOSOCIAL ONCOLOGIC CARE AND DISPARITIES

At Montefiore Einstein Center for Cancer Care in the Bronx, New York, our renowned basic science and clinical research teams are advancing personalized cancer care by developing tools to better predict the likely course of a person’s cancer to provide the right therapy at the right time to each person. Why can’t we use the same approach to address a patient’s psychosocial needs?

To chart a new path for comprehensive cancer care, Edward Chu, MD, MMS, our cancer center director, is leading scientific approaches such as community-based participatory research and using patient preference trials to study interventions that will best meet patient needs.

These approaches are the center of the “gold standard” in medical research—the randomized controlled trial—and include patient voices in determining which outcomes and interventions are most important to the community.

In our clinical trial design, patient advocates and community advisory boards are common components. Further, in our research, patients serve as guides in addressing racial and ethnic disparities as well as ensuring our suite of therapeutic approaches are culturally appropriate.

Since 2007, my team has evaluated the preferences of more than 2500 patients with cancer to identify which psychosocial modalities our patients find most helpful. Therapies range from individual counseling, support groups, spiritual support, mind-body therapies, and conversations with cancer survivors.

Collecting patient information and preferences is extremely important, particularly in our Bronx community, which is home to one of the most economically disadvantaged counties in the country. It is also the least healthy county in New York State.

By identifying the services our participants say they need, we can provide these essentials. We can also remove the barriers that interfere with their ability to access medical care and mental health services and adhere to their treatment.
TARGETED APPROACH TO MIND-BODY THERAPIES

A community-based participatory model was leveraged to launch our psycho-oncology research program from the point of greatest interest to our Bronx cancer community—mind-body interventions. With scientific rigor and cultural competency, our early work started with a National Cancer Institute–funded randomized controlled trial\(^1\) comparing a group yoga intervention with a wait list control group to examine the effect of yoga on quality of life among English- and Spanish-speaking patients with breast cancer. Our findings indicated that yoga had a significant impact on our patients’ social well-being.

We then conducted a patient preference trial\(^2\) in which we queried underserved patients with cancer about their choice of a spiritually oriented support group vs a psychoeducational support group. Then, we randomized these individuals during an initial 12-week intervention phase. Following the trial, we gave participants the option to enroll in their preferred group. Not surprisingly, we found greater engagement and satisfaction among those who had received their support group of preference.

In a pilot trial\(^3\) of a 20-week group meditation program with underserved, primarily minority patients with breast cancer, participants reported significant improvement in overall quality of life with particular benefits to social well-being, as mirrored in our earlier yoga study.

PEER-DELIVERED MEDITATION AND BEYOND

As we continue to innovate in the area of mind-body research, our psycho-oncology team recently published the findings of a pilot study\(^4\) of loving kindness meditation delivered through peer navigators. These are volunteers who are survivors of cancer or professional meditation teachers.

Results showed that patients were as satisfied with peer navigators as they were with the professional meditation teachers. Additionally, they experienced similar benefits in emotional well-being, with a 15% increase in positive moods and 9% decrease in negative moods, as well as a significant increase in relaxation response. Moreover, 100% of the volunteers reported feeling comfortable incorporating this new mind-body intervention into their role as peer navigators.

In addition to meditation’s positive impact on quality of life, the study results demonstrate that this may be a novel approach to patient empowerment, particularly among disenfranchised populations. All peer navigators and 85% of the patients were from low-income, ethnic minority groups and both were faced with the stresses of a diagnosis of cancer. The bilateral effects of this peer-delivered intervention offer an important example of moving from improvement to empowerment in the experience of cancer survivorship. After participating in learning and delivering loving kindness meditation, our cancer survivor volunteers reported feeling “at peace,” “useful,” “calm,” “good/great,” and “present.” One volunteer shared, “This is an awesome technique that can heal the patient and leader.”

Looking ahead, we are aiming to advance our research of targeted patient care through a randomized patient-preference trial. The trial will incorporate patients’ choice of mind-body modality with peer navigator and professional delivery and expand the evaluation of the intervention beyond psychosocial outcomes to include medical adherence and engagement. We will also investigate healing energy modalities, such as Reiki, during medical procedures. In addition, we will be enlisting medical students to act as patient navigators so these future clinicians can appreciate the challenges of navigating cancer care decisions for patients and their families.

With the impact of COVID-19, our ongoing psychosocial needs assessment initiative continues to point us in the direction of our patients’ priorities. In particular, it has highlighted the great isolation and anxiety that patients with a new diagnosis of cancer face during the pandemic. In response, studies on virtual peer navigation are underway.

In the end, the goal of targeted patient care may best be described as the attempt to create the optimal healing environment. That is one in which “patients and families come to health care providers with hopes, expectations, and beliefs [and] healing intention can be manifest in care through holistic assessment… and incorporating those hopes into the plan of care.”\(^5\)

**REFERENCES**

Novel Triplets Shed New Light on Sequencing in Relapsed/Refractory Myeloma

by BRITTANY LOVELY

NEW TRIPLET COMBINATIONS ANCHORED by anti-CD38 antibodies are expanding the therapeutic landscape for relapsed or refractory (R/R) multiple myeloma, providing exciting options that extend progression-free survival (PFS) windows from months to years for heavily pretreated patients, according to a panel of hematologic experts. Nevertheless, the regimens come with complex questions about how best to sequence and personalize treatment.

In August 2020, the FDA approved a new indication for KdD—daratumumab (Darzalex), a CD38-directed monoclonal antibody in combination with carfilzomib (Kyprolis) plus dexamethasone—for adult patients with R/R multiple myeloma who have previously received 1 to 3 lines of therapy.1 In March, the FDA approved isatuximab-irfc (Sarclisa), another anti-CD38 antibody, in combination with Kd–carfilzomib plus dexamethasone—also for the treatment of adult patients with R/R multiple myeloma who have previously received 1 to 3 lines of therapy.2

Daratumumab and isatuximab both were previously approved in the R/R setting in combination with pomalidomide (Pomalyst), an immunomodulatory drug (IMiD), plus dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including the IMiD lenalidomide (Revlimid) and a proteasome inhibitor (PI).

“We’ve made a lot of progress with induction therapy, transplant, and lenalidomide maintenance therapy,” said Ajai Chari, MD, during a recent OncLive® The Talk program on multiple myeloma. “Unfortunately, in the relapsed setting many patients are lenalidomide refractory. I think what’s not well appreciated is how that independently is a negative prognostic factor even with regimens that do not contain lenalidomide.”

However, as triplets continue to stake their claim in the armamentarium, exploratory analyses seek to offer more answers for individualized treatment considerations, including prior therapy, comorbidities, and perhaps the identification of future predictive markers.

Chari moderated the discussion based on the latest data from the 62nd American Society of Hematology Annual Meeting and Exposition in December 2020, which include findings from these pivotal studies involving patients with R/R multiple myeloma:

- **CANDOR (NCT03158688):** a phase 3 study that compared KdD with Kd in patients who relapsed after 1 to 3 prior lines of therapy3;
• **IKEMA (NCT03275285):** a phase 3 study that compared the combination of isatuximab, carfilzomib plus dexamethasone with Kd, also in patients who relapsed after 1 to 3 prior lines of therapy; and

• **APOLLO (NCT03180736):** a phase 3 study that evaluated subcutaneous daratumumab (Darzalex Faspro) plus pomalidomide vs pomalidomide alone in patients who received at least 1 prior line of therapy including lenalidomide and a PI.5

Panelists C. Ola Landgren, MD, PhD; Saad Usmani, MD; and Meletios A. Dimopoulos, MD, joined Chari to unpack the role of these regimens, including dosing considerations, for patients with advanced disease.

**CHARI**
Moving to a very complicated part of the disease, because of the increasing drug availability, let’s discuss updates in relapsed or refractory myeloma. Let’s get things started with Dr Dimopoulos, who has some very exciting updates on the combination of daratumumab, carfilzomib, and dexamethasone.

**DIMOPOULOS**
Yes, the [CANDOR] trial, which Dr Usmani had a very significant role in the design and the conduction of the follow-up of the study, compared KdD [versus] Kd given on the approved schedule of 56 mg for 2 consecutive days. The main finding of this study and the follow-up was that there was a significant improvement, a sustained improvement, in PFS in favor of KdD.

Of particular interest were the patients who were pretreated with lenalidomide and those who progressed on lenalidomide, where we saw, for the first time, a median PFS exceeding 2 years in this specific subset of patients. This is the best PFS that we have seen. We know that Kd and daratumumab/carfilzomib/dexamethasone are really not optimal for these patients with a median PFS of [typically] no more than 10 months. We have seen some improvement [in PFS] with pomalidomide/carfilzomib/dexamethasone of up to 18 months, and now a PFS of 26 to 28 months is really encouraging [TABLE1].

Dr Usmani, you published these data recently, congratulations. Any comments on other updates that you heard about at ASH on CANDOR?

**USMANI**
I think from a practical standpoint, one of the things that we struggle with is treating patients who are lenalidomide refractory in the US because many patients receive lenalidomide maintenance. The data for the lenalidomide refractory population are probably the key takeaway for me. Many of us have been big fans of the data on the dexamethasone combination for that patient population based on the phase 1b experience that you had published, Dr Chari.

But daratumumab plus Kd adds a very good alternative to that particular regimen and speaks to that class switch that we had talked about for 15 years when all we had were the first-generation PIs and IMiDs.

The depth of response data that Dr Landgren shared was also very encouraging. CANDOR was the first study that looked at a time-dependent MRD [minimal residual disease]-negative CR [complete response] rate at 12 months. That’s keeping in mind the International Myeloma Working Group response criteria. These data showed very good MRD-negative CR rates with sustained MRD negativity, as well, and that’s something unique to this 3-drug combination.

**CHARI**
Dr Landgren, any more thoughts on your presentation? And perhaps you could share the data for IKEMA study?

**LANDGREN**
[The data from the] CANDOR study showed that the PFS rates for patients who

---

**TABLE.** Updated Efficacy Data of Triplet Combos for Patients With Relapsed or Refractory Multiple Myeloma 1-6

<table>
<thead>
<tr>
<th>studies</th>
<th>study name</th>
<th>phase</th>
<th>comparator</th>
<th>regimen</th>
<th>Approval</th>
<th>Outcome</th>
<th>Median PFS*, months</th>
<th>Best overall MRD-negative CR rate6</th>
<th>MRD-negative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKEMA</td>
<td>(NCT03275285): isatuximab-irfc plus Kd vs Kd in patients with multiple myeloma who have relapsed after 1 to 3 prior lines of therapy</td>
<td>3</td>
<td>Kd</td>
<td>Isatuximab + Kd (n = 179)</td>
<td>Approval: March 31, 2021</td>
<td>Outcome</td>
<td>Isatuximab + Kd</td>
<td>86.6%</td>
<td>29.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kd (n = 123)</td>
<td></td>
<td></td>
<td></td>
<td>82.9%</td>
<td>13.0%</td>
</tr>
<tr>
<td>CANDOR</td>
<td>(NCT03158688): KdD vs Kd in patients with multiple myeloma who have relapsed after 1 to 3 prior lines of therapy</td>
<td>3</td>
<td>Kd</td>
<td>KdD (n = 312)</td>
<td>Approval: August 20, 2020</td>
<td>Outcome</td>
<td>KdD</td>
<td>28.6 (HR, 0.59; 95% CI, 0.45-0.78)</td>
<td>13.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kd (n = 154)</td>
<td></td>
<td></td>
<td></td>
<td>15.2</td>
<td>5.8%</td>
</tr>
<tr>
<td>APOLLO</td>
<td>(NCT03180736): subcutaneous daratumumab plus pomalidomide vs pomalidomide alone in patients with relapsed or refractory patients with multiple myeloma who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor</td>
<td>3</td>
<td>Pomalidomide</td>
<td>Daratumumab + pomalidomide (n = 151)</td>
<td>Approval: Regulatory application filed November 12, 2020</td>
<td>Outcome</td>
<td>Daratumumab + pomalidomide</td>
<td>12.4</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pomalidomide (n = 153)</td>
<td></td>
<td></td>
<td></td>
<td>6.9</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR</th>
<th>ORR</th>
<th>MRD-negative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete response; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; NR, not reached; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*PFS evaluated using Onyx Response Computer Algorithm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*At any point.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Many feel that daratumumab and isatuximab are similar in the delta and the difference in the experimental arms, there are a lot of similarities in the standard-of-care arms of the study and the experimental arms, there are a lot of similarities in the delta and the difference that you’re seeing.

You know when you add an anti-CD38 agent to Kd, you’re going to get good responses. I would be keen to look into the lenalidomide-refractory population specifically, as well as the high-risk population and see what the differences are there as the data mature on both these studies.

Let’s get into the dosing a little bit because I think that’s really important. The dosing in the ENDEAVOR trial was 56 mg twice weekly as compared with the 70 mg weekly in the A.R.R.O.W. trial [NCT02412878]. Both CANDOR and IKEMA were building on ENDEAVOR (and used) 56 mg twice weekly. What do you all use in practice?

Depending on the patient, it’s either 56 mg weekly or 70 mg weekly. Again, based on the famous Dr Chari phase 1 experiment with daratumumab and Kd, I think it depends on the clinical situation and what the patient can tolerate, but in general I haven’t found any difference in efficacy in my patients.

We use 70 [mg]. I think the concern [about whether] to lower the dose of carfilzomib on a weekly basis [depends on] when we combine it with lenalidomide. Without lenalidomide, we feel pretty comfortable to use 70 mg with anti-CD38 monoclonal antibodies.

I’ll just add that we did an analysis comparing the weekly 70-mg [dose] vs the twice weekly 56-mg [dose] in CANDOR and the outcomes were comparable. From a cost perspective, it’s actually [less expensive] because 70 mg weekly is less drug than 56 mg twice weekly. I think that is something to keep in mind.

But let’s move on to perhaps one of the most eagerly awaited abstracts for relapsed or refractory disease, which Dr Dimopoulos presented beautifully.

This is the APOLLO trial of daratumumab/pomalidomide/dexamethasone vs pomalidomide/dexamethasone.

For this particular study, first we have to clarify that the patient population [had more advanced disease] than the CANDOR or the IKEMA studies, where half of the patients received only 1 prior line of therapy. In the APOLLO trial, patients had to be refractory progressing on both lenalidomide and bortezomib. However, 10% of the patients had received 1 prior line of therapy.

These were patients who have received [bortezomib/lenalidomide/dexamethasone] and who have progressed. The results of this study confirmed what your study, Dr Chari, had shown several years ago: the large phase 2 study [NCT01998971; EQUULEUS], which led to the approval of daratumumab/pomalidomide/dexamethasone in the United States.

APOLLO was a formal prospective randomized trial that needed to demonstrate that this treatment was more active than pomalidomide/dexamethasone, as well as [to provide the] opportunity for this treatment to be approved outside the United States. That was the main end point, and results showed an improvement in PFS with an HR of 0.68. Additionally, the toxicity profile was acceptable with a slight increase in grade 3 or 4 neutropenia and the rate of infections, especially pneumonias.

This study established daratumumab/pomalidomide/dexamethasone as a salvage therapy for patients who have received at least 1 [prior line of therapy], but most of the patients had received a median of 2 lines of therapy. Hopefully, the results will lead to the approval of this combination outside the United States.

Dr Usmani, you referred earlier to daratumumab/pomalidomide/dexamethasone as one of your go-to regimens. How do these results compare with what you were expecting?

I agree with Dr Dimopoulos’ comment about the APOLLO study having a more advanced patient population than CANDOR or IKEMA and probably the same is true for those data that were presented last year. You know my
To see if your patient is clearing MTX as expected, visit **MTXPK.org**.

This free, independently developed clinical decision-making tool provides patient-specific expected and actual elimination curves, along with serum creatinine trends and time to attain threshold levels for discharge planning.

Enter patient dosing information and known lab values to display the MTX Elimination Curve.

No log in required. No patient data stored.

This tool has been validated for use with adult and pediatric patients based on over 47,000 MTX concentration levels in 1,800 patients.
general impression of daratumumab/pomalidomide/dexamethasone—if used in earlier line of treatment [it] was somewhat similar to the experience that you had shared. I think even in the MM 014 study [NCT01946477] for earlier lines of daratumumab/pomalidomide/dexamethasone use, the median PFS was north of 20 months for those patients, and they were all lenalidomide refractory. I was a bit surprised that you would see that kind of an overall drop in PFS.

But I suspect it probably has to do with how refractory patients were and that they had more median lines of treatment. I was surprised [by the results]; I was expecting similar results from APOLLO as we had seen with CANDOR, for example. I was a little underwhelmed with the outcomes.

Every study population is different, so if you have more or less patients [with advanced disease], that is going to always affect the results. That’s why you can never compare results across studies. We already know it, but we do it all the time, and we always ask the same question, but that is the simple answer. It also reminds me of the fact that we are probably going to see more of these types of studies because there are more drugs.

It is going to be harder to develop new therapies in the future because patients [who progress] to later lines have gone through so many more therapies. I think we could maybe project in the future that the differences may not be as profound as they used to be in the past because of the fact [that we have] more drugs available. It will obviously dilute [data] on the back end, and there will not be overall survival differences because patients are going to go through every therapy in the end.

In general, development in the field is changing. So, to answer your question, I use the best drugs up front, but what do I do if the disease comes back? Well, I do the same thing again—I’m sure you do the same: I give the best drugs up front, go to maintenance, then, of course, patients [have] PFS for so long, for say, 5, 6, 7, 8, 9 years. If the disease progresses, I give the same drugs 1 more time, they work 1 more time. Just because you gave a therapy up front doesn’t mean that it doesn’t work later.

If you give a drug and the disease progresses and you start 6 months later with the same therapy, of course that’s not going to work. But if you have years between treatments, it’s not a problem clinically. Therefore, I give the best drugs every time.

Who would be the ideal candidate for a CD38 antibody in combination with pomalidomide/dexamethasone?

I believe that patients who progress on bortezomib/lenalidomide/dexamethasone may be treated with an anti-CD38 [anti-body]/pomalidomide/dexamethasone. Based on the data from the IKEMA and CANDOR studies, I am more in favor [of using those regimens in] earlier lines of therapy. Then, for patients who have more advanced disease, I would use the other [available] treatments. However, we’ve been seeing more patients who progress on both lenalidomide and daratumumab. In that setting, a type of treatment such as carfilzomib/pomalidomide/dexamethasone may be of interest.

I think what we are seeing here is that the pomalidomide/dexamethasone backbone was perhaps just a little bit disappointing for this population. And, again, we caution that they are much more heavily treated patients, more double refractory. So it’s not appropriate to compare, but it brings up the question of class switching. If you [see a patient who is progressing] on lenalidomide, should you switch to carfilzomib?

I think [there are] very compelling data for Kd. Further, a CD38 antibody plus pomalidomide/dexamethasone would be another option.

The last point, of course, is keeping in mind toxicity. I think carfilzomib’s cardiac toxicity is often overblown. We know that the response and PFS and OS are superior in several phase 3 studies, which means that it’s generally well tolerated and risks are outweighed by the benefits. However, for really elderly patients—those with known cardiac dysfunction, uncontrolled blood pressure—there may be a role for pomalidomide. Conversely, individuals who are very cytopenic or prone to infections may be better suited for carfilzomib, based on what we saw.

It’s nice to have options, nice to have some data, and I think [when it comes to] sequencing, which is such a difficult option, we’re finally getting to see some light.

REFERENCES


Strategies for Targeting PI3K Proliferate

by JANE DE LARTIGUE, PHD

FREQUENTLY DYSREGULATED IN CANCER CELLS, the PI3K pathway has long been a high-priority therapeutic target in oncology. However, initial efforts with pan–class I PI3K inhibitors were hampered by disappointing efficacy and substantial toxicity.

The shift to isoform-specific inhibitors yielded more success, with several PI3Kα inhibitors and the first PI3Kδ inhibitor, alpelisib (Piqray), now approved by the FDA.

Several other pan–class I PI3K inhibitors were hampered by disappointing efficacy and substantial toxicity.

The most recent addition to the armamentarium, umbralisib (Ukoniq), is a dual inhibitor of PI3Kδ and casein kinase-1α (CK1α). With umbralisib approved by the FDA in February for the treatment of relapsed/refractory marginal zone lymphoma (MZL) and follicular lymphoma (FL), TG Therapeutics, Inc has also filed for approval of the agent combined with the company’s anti-CD20 antibody, ublituximab, to treat patients with chronic lymphocytic leukemia (CLL) based on topline data from the UNITY-CLL trial.

A host of other PI3K Inhibitors designed to further improve the safety and efficacy of this drug class are being evaluated in clinical trials (TABLE). Meanwhile, indications for PI3K inhibitors could soon expand beyond B-cell malignancies and breast cancer, with promising signals from the development of the PI3Kγ inhibitor eganelisib (IPI-549) in combination with nivolumab (Opdivo) for the treatment of patients with metastatic urothelial carcinoma.

TOXICITY HAMPPERS EARLY EFFORTS

Although initial efforts to develop inhibitors targeting all of the class I PI3K isoforms were largely abandoned, copanlisib (Aliqopa) has emerged as a notable exception. In 2017, the FDA approved the kinase inhibitor for the treatment of adult patients with relapsed/refractory FL in the third-line setting.

Although copanlisib is described as a pan–class I PI3K inhibitor, it most potently inhibits PI3Ka and PI3Kδ.

Several other pan–class I PI3K inhibitors are still in development. Buparlisib (BK12) has been studied extensively in several tumor types, including breast cancer, culminating in the phase 3 BELLE-3 trial (NCT01633060). In BELLE-3, the combination of buparlisib plus fulvestrant (Faslodex) demonstrated improved progression-free survival (PFS) compared with placebo plus fulvestrant, but at the expense of substantial toxicity that precluded further development in this setting.

Worldwide development and commercialization rights for buparlisib were transferred from Novartis to the Chinese firm Adlai Nortye in July 2018. Buparlisib demonstrated promise in combination with paclitaxel for the treatment of platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in the phase 2 BERIL-1 study (NCT01852292), and Adlai Nortye has initiated the phase 3 BURAN trial (NCT04330399) of this combination in patients with HNSCC that progressed after prior platinum-based chemotherapy with or without prior PD-1/PD-L1 inhibitor treatment.

Other early efforts focused on dual inhibitors of PI3K (pan–class I) and its downstream target mTOR; these drugs largely suffered a fate similar to that of pan–class I inhibitors. Several continue to be evaluated in clinical trials, however; notable among them is the oral PI3K/mTOR inhibitor paxalisib (GDC-0084). Most current clinical trials of this agent, which penetrates the blood-brain barrier, are in brain cancer; PI3K pathway upregulation has been demonstrated in 85% of glioblastoma cases.

Paxalisib is being evaluated in patients with newly diagnosed glioblastoma and unmethylated MGMT promoter status in an ongoing phase 2 trial (NCT03522298).

Results of an interim analysis showed a median PFS of 8.4 months and overall survival of 17.5 months among 24 patients treated at the maximum-tolerated dose of 60 mg. The most common toxicities were rash, stomatitis, hyperglycemia, fatigue, nausea, and decreased appetite.

HEMATOLOGIC MALIGNANCIES

Attention in the field has largely gravitated toward isoform-specific inhibitors in the hopes of reducing off-target toxicity. Expression of the PI3Kδ and PI3Kγ isoforms is enriched in hematopoietic cells, leading to the pursuit of PI3Kδ/γ–specific inhibitors in patients with hematologic malignancies.

This quest culminated in the first FDA approval of a PI3K inhibitor in 2014. Idelalisib (Zydelig), an oral PI3Kδ inhibitor, was approved for the treatment of patients with relapsed/refractory small lymphocytic lymphoma (SLL) and FL and in combination with the CD20-targeting antibody rituximab (Rituxan) for the treatment of patients with relapsed/refractory CLL. Then, in 2018, the FDA approved the oral PI3Kδ/γ inhibitor duvelisib (Copiktra) for the treatment of adult patients with relapsed/refractory CLL, SLL, or FL.

Most recently in this category, umbralisib was approved for the treatment of adult patients with relapsed/refractory MZL who have received at least 1 prior CD20 antibody–based regimen and those with relapsed/refractory FL previously treated with at least 3 lines of systemic therapy.

Umbralisib has a novel chemical structure, which is designed to reduce the potential for hepatotoxicity but also results in potent inhibition of CK1ε in addition to PI3Kδ. Combined inhibition of these 2 kinases has shown synergistic activity preclinically, with enhanced killing of lymphoma cells.

FDA approval was based on the MZL and FL single-arm cohorts of the UNITY-NHL trial (NCT02793583). Patients with relapsed/refractory MZL (n = 69), FL (n = 117), or SLL (n = 22) were treated with 800-mg once-daily umbralisib. Objective response rates (ORRs) were 49.3%, 45.3%, and 50.0% in patients with MZL, FL, and SLL, respectively, with complete responses (CRs) in 16%, 5%, and 5%.
PI3K ENZYMES HELP CONTROL myriad cellular functions by facilitating intracellular signaling through the phosphorylation of inositol lipids contained within cell membranes. The PI3K family encompasses numerous isoforms, which are categorized into 3 classes; there are 4 class I isoforms, 3 class II isoforms, and a single class III isoform.2-4

The class I PI3Ks are the most clearly implicated in the development of cancer.2 In response to upstream activation by various membrane-bound receptors, class I PI3Ks are activated, phosphorylating PI2P to form PI3P, which recruits a wide range of proteins to the plasma membrane through specific lipid-binding domains, such as pleckstrin homology domains (FIGURE 1). The most renowned of these downstream targets is the serine/threonine kinase AKT, which subsequently further propagates the signal downstream through its own kinase activity.2,4

Class I PI3Ks are further subdivided into 3 class IA PI3Ks and 1 class IB PI3K, each of which is a heterodimer consisting of a catalytic subunit paired with a regulatory subunit. The class IA catalytic subunits p110α, p110β, and p110δ are encoded by the PIK3CA, PIK3CB, and PIK3CD genes, and they bind to 1 of 5 regulatory subunits, p85α (or a shorter splice variant, p55α or p50α), p85β, or p55γ, which are encoded by the PIK3R1, PIK3R2, and PIK3R3 genes, respectively, thus forming the PI3Kα, β, and δ isoforms. The class IB PI3K, PIK3y, is composed of the p110y catalytic subunit (encoded by PIK3CG) bound to either the p101 or p87 regulatory subunit (encoded by PIK3R5 and PIK3R6).2-4

Upon activation of the PI3K, the regulatory subunit releases its inhibitory contacts and enables the enzyme to perform its catalytic function. The activity of the class I PI3Ks is counterbalanced by the lipid phosphatase PTEN, which converts PI3P back to PI4P and terminates PI3K signaling.2-4

The PI3K pathway is among the most frequently altered signal-pathways in human cancer; an estimated 30% to 50% of tumors have aberrations in PI3K pathway components.2 PI3K signaling can be dysregulated via a number of mechanisms, most notably via activating mutations in the PI3KCA oncogene.2-4 According to a meta-analysis of cancer genome sequencing studies, PIK3CA is the second most highly mutated gene in human cancers.1

Aberrant PI3K pathway activation in cancer can occur via a wide variety of other mechanisms, among them inactivating mutations in the tumor suppressor PTEN,2,4 which is the third most commonly mutated gene in cancer.1

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

FIGURE. Main Elements of the PI3K Pathway2

Mutations in kinases in the PI3K pathway along with decreased expression of PTEN are significant factors that promote neoplastic activity. Pathogenic signaling also can occur through G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs).


The most common any-grade adverse events (AEs) included diarrhea, nausea, and fatigue, and grade 3/4 AEs included neutropenia, diarrhea, and alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations.22

Topline data from the ongoing UNITY-CLL trial (NCT02612311) were recently presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition in December 2020. In this study, umbralisib in combination with the CD20-targeted antibody ublituximab is compared against a combination of obinutuzumab (Gazyva) plus chlorambucil in patients with treatment-naïve or relapsed/refractory CLL.a

At a median follow-up of 36.7 months, the median PFS was 31.9 months (95% CI, 28.2-35.8 months) in the umbralisib/ublituximab arm vs 17.9 months (95% CI, 16.0-22.6 months) in the comparator arm (HR, 0.55; 95% CI, 0.41-0.72; P < .0001). ORR was also significantly higher in the umbralisib/ublituximab arm compared with the obinutuzumab/chlorambucil arm (P < .001), with numerical superiority in both treatment-naïve and previously treated patients. Responses were durable, with 62% of umbralisib/ublituximab responses maintained at 2 years.a

The most common grade 3/4 AEs included neutropenia and diarrhea.3 In December 2020, TG Therapeutics initiated a rolling submission of a biologics license application to the FDA seeking approval of this combination in patients with CLL.a
### TABLE. Select PI3K Inhibitors in Clinical Development

<table>
<thead>
<tr>
<th>Agent (brand name if applicable; developer)</th>
<th>Development stage/ongoing clinical trials and settings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI3Kα inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Alpelisib (Piqray; Novartis)</td>
<td>FDA approval (2019): in combination with fulvestrant in HR+, HER2-, PIK3CA-mutated advanced/metastatic breast cancer after progression on or after endocrine therapy</td>
</tr>
<tr>
<td></td>
<td>Phase 3: HER2+ breast cancer; TNBC; serous ovarian cancer*</td>
</tr>
<tr>
<td></td>
<td>Phase 2: HPV-associated oropharyngeal cancer</td>
</tr>
<tr>
<td>Inavolisib (GDC-0077; Genentech)</td>
<td>Phase 2/3: HR+, HER2- metastatic breast cancer</td>
</tr>
<tr>
<td>Serabelisib (TAK-117; Takeda/Petra Pharma)</td>
<td>Phase 1/2: metastatic advanced solid tumors*</td>
</tr>
<tr>
<td>CYH33 (Haihe Biopharma)</td>
<td>Phase 1: advanced solid tumors</td>
</tr>
<tr>
<td><strong>PI3Kβ inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>GSK2636771 (GlaxoSmithKline)</td>
<td>Phase 2/3: HR+, HER2- metastatic breast cancer</td>
</tr>
<tr>
<td><strong>PI3Kβ/δ inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>AZD8186 (AstraZeneca)</td>
<td>Phase 2: advanced gastric cancer</td>
</tr>
<tr>
<td><strong>PI3Kδ inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Idelalisib (Zydelig; Gilead)</td>
<td>FDA approval (2014): in combination with rituximab for patients with relapsed/refractory CLL and as monotherapy for patients with relapsed/refractory SLL/FL who have received at least 2 prior systemic therapies</td>
</tr>
<tr>
<td></td>
<td>Phase 2: FL; DLBCL; CLL/SLL; Waldenström macrogobulinemiaa</td>
</tr>
<tr>
<td>Parsaclisib (Incyte)</td>
<td>Phase 3: myelofibrosis</td>
</tr>
<tr>
<td>Zandelisib (ME-401; MEI Pharma)</td>
<td>Phase 2: FL; DLBCL; CLL/SLL; MZL</td>
</tr>
<tr>
<td>BGB-10188 (BeiGene)</td>
<td>Phase 1/2: advanced malignancies</td>
</tr>
<tr>
<td><strong>PI3Kγ inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Idelalisib (Zydelig; Gilead)</td>
<td>FDA approval (2014): in combination with rituximab for patients with relapsed/refractory CLL and as monotherapy for patients with relapsed/refractory SLL/FL who have received at least 2 prior systemic therapies</td>
</tr>
<tr>
<td></td>
<td>Phase 2: FL; DLBCL; CLL/SLL; Waldenström macrogobulinemiaa</td>
</tr>
<tr>
<td><strong>Pan-PI3K Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Copanlisib (Aliqopa; Bayer HealthCare Pharmaceuticals)</td>
<td>FDA approval (2017): for adult patients with relapsed/refractory MZL who have received at least 1 prior anti-CD20-based regimen or with relapsed/refractory FL who have received at least 3 prior lines of therapy</td>
</tr>
<tr>
<td></td>
<td>Phase 2/3: NHL</td>
</tr>
<tr>
<td></td>
<td>Phase 2: FL; CLL; classical HL; MCL</td>
</tr>
<tr>
<td>Men1611 (Menarini Ricerche)</td>
<td>Phase 1/2: mCRC</td>
</tr>
<tr>
<td>Buparlisib (BK120; Adlai Nortye)</td>
<td>Phase 3: HNSCC</td>
</tr>
<tr>
<td>Fimepinostat (CUDC-907; Curis, Inc)</td>
<td>Phase 1: pediatric solid tumors, CNS tumors, or lymphomas</td>
</tr>
<tr>
<td><strong>PI3K/mTOR inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Samotolisib (LY3023414; Eli Lilly and Company)</td>
<td>Phase 2: advanced cancers with mutations in PI3K/mTOR pathway genes; metastatic TNBC</td>
</tr>
<tr>
<td>Paxalisib (GDC-0804; Kazia Therapeutics)</td>
<td>Phase 2/3: MGMT-unmethylated glioblastoma</td>
</tr>
<tr>
<td>Apitolisib (GDC-0980; Genentech)</td>
<td>Phase 1/2: mCRPC</td>
</tr>
</tbody>
</table>

*Not yet recruiting.  
*Trial is active but no longer recruiting.  
*Umbralisib also inhibits caspin kinase-1e.  
*MEN1611 inhibits all class I PI3K isoforms, except PI3Kδ.  
*Fimepinostat inhibits all class I PI3K isoforms, except PI3Kγ, and also inhibits histone deacetylases.

**CLL**, chronic lymphocytic leukemia; CNS, central nervous system; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HR, hormone receptor; MCL, mantle cell lymphoma; mCRPC, metastatic castration-resistant prostate cancer; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma; TNBC, triple-negative breast cancer.
Among other PI3Kα inhibitors in development, parsaclisib has more than 19,000-fold selectivity for PI3Kα over other class I isoforms. Similar to umbralisib, it has a novel structure designed to reduce hepatotoxicity.23 Preliminary results were presented at 2020 ASH. Patients with relapsed/refractory FL, MZL, and mantle cell lymphoma (MCL) were treated, respectively, in the CITADEL-203 (NCT03126019), CITADEL-204 (NCT03144674), and CITADEL-205 (NCT03235544) studies with parsaclisib at 20 mg once daily for 8 weeks, followed by either 20 mg once weekly or 2.5 mg once daily. As of January 2020, 106 patients with FL (22 with weekly dosing, 84 with daily dosing), 99 patients with MZL (28 weekly, 71 daily), and 151 patients with MCL (43 weekly, 108 daily) had received treatment.24-27

Patients with MZL had received 1 or more prior therapies, including a CD20-targeted antibody, but had not been treated with a Bruton tyrosine kinase (BTK) inhibitor, whereas those with MCL were stratified according to prior receipt of a BTK inhibitor, such as ibrutinib (Imbruvica). ORRs were 69.8% and 54.3% in patients with FL and MZL, respectively, and 28.3% and 66.3% in patients with MCL who were previously treated with ibrutinib (n = 47) vs those who were not (n = 104).24-27

Meanwhile, MEI Pharma, Inc is developing the oral PI3Kα inhibitor zandelisib (ME-401). In the phase 3 COASTAL study (NCT04745832), patients with indolent non-Hodgkin lymphoma are treated with zandelisib in combination with rituximab. Zandelisib was awarded fast track designation for the treatment of adult patients with relapsed/refractory FL in March 2020.28

**PI3Kα INHIBITORS IN BREAST CANCER**

The **PIK3CA** gene, which encodes the p110α catalytic subunit of the PI3Kα isoform, is among the most commonly mutated genes in human cancer,29 including approximately 40% of patients with hormone receptor-positive, HER2-negative breast cancer, and has been shown to be a driver of resistance to endocrine therapy, the cornerstone of treatment in this cancer type.30 In May 2019, alpelisib became the first FDA-approved PI3Kα inhibitor. The agent is approved in combination with fulvestrant for the treatment of patients with hormone receptor-positive, HER2-negative, **PIK3CA**-mutant advanced or metastatic breast cancer following progression on or after endocrine therapy. Approval was based on results from the phase 3 SOLAR-1 trial (NCT02437318), in which the combination prolonged PFS compared with placebo plus fulvestrant (median PFS, 11.0 months vs 5.7 months; HR, 0.65; 95% CI, 0.50–0.85; P < .001). The most common grade 3/4 AEs were hyperglycemia and rash; both were more common in the alpelisib arm.31 Alpelisib is approved only for patients with **PIK3CA**-mutant tumors, as determined by 1 of 3 FDA-approved companion diagnostic tests: Giagien’s *therascreen* **PIK3CA** RQG PCR Kit, a real-time, qualitative, single-gene polymerase chain reaction test that detects 11 mutations in the **PIK3CA** gene, and Foundation Medicine’s FoundationOne CDx and FoundationOne Liquid CDx, which are comprehensive genomic profiling tests that use next-generation sequencing to assess multiple genes, including **PIK3CA**. Giagien’s test can be performed on both tissue and plasma, and the 2 FoundationOne tests are for tissue and plasma testing, respectively.32

In recent years, CDK inhibitors have become a new part of standard care in hormone receptor-positive, HER2-negative breast cancer. Thus, the ongoing phase 2 BYLieve trial (NCT03056755) is evaluating alpelisib in combination with fulvestrant in patients whose most recent prior treatment was a CDK4/6 inhibitor plus an aromatase inhibitor (cohort A; n = 127) or alpelisib plus letrozole in those last treated with a CDK4/6 inhibitor and fulvestrant (cohort B; n = 126). The primary end point was met in both cohorts, with 30.4% (95% CI, 41.2%-59.6%) and 46.1% (95% CI, 36.8%-55.6%), respectively, of patients alive without disease progression at 6 months. The safety profile was manageable.33,34 A number of other PI3Kα inhibitors are in development, including serabelisib (TAK-117; Takeda Pharmaceutical licensed in 2019 to Petra Pharma Corporation35). Results from the dose-escalation portion of a phase 1b trial (NCT03154294) of serabelisib in combination with the TORC1/2 inhibitor sapanisertib (TAK-228) and paclitaxel in patients with advanced ovarian, endometrial, or breast cancer demonstrated an ORR of 46% in 13 evaluable patients, with 2 patients achieving CRs.36

Efforts also are underway to develop drugs specifically targeting mutant forms of PI3Kα to reduce the potential for off-target toxicity. Genentech’s inavolisib (CDC-0077) is a novel oral PI3Kα inhibitor that also degrades the mutant form of the protein.37 Among 20 patients treated with escalating doses of inavolisib monotherapy in an ongoing phase 1 trial (NCT03006172) in patients with advanced **PIK3CA**-mutant solid tumors, the clinical benefit rate was 45%, with partial responses in 5 patients. Grade 3 and higher treatment-related AEs included hyperglycemia, lymphopenia, fatigue, nausea, weight loss, and asthenia.38

**EXPANDING TUMOR TYPES**

Eganelisib is another notable agent in clinical development that could expand the approved uses of this drug class in the near future. An oral PI3Kγ inhibitor, eganelisib is being evaluated in combination with nivolumab in patients with metastatic urothelial carcinoma in the ongoing phase 2 MARIO-275 trial (NCT03980041).

Preliminary data showed that, among 33 patients who received nivolumab plus eganelisib, the ORR was 30.3%, compared with 25.0% in 16 patients who received nivolumab plus placebo, and the median PFS was 9.1 vs 8.0 weeks, respectively. In this patient population, low or negative tumor PD-L1 expression is generally associated with a poor response to immune checkpoint inhibitor monotherapy. The investigators noted that the eganelisib combination gave a particularly strong efficacy boost to patients with PD-L1-negative tumors, with an ORR of 26% vs 14% in the nivolumab-alone arm and a disease control rate of 57% vs 14%. Eganelisib was well tolerated at a dose of 30 mg once daily.39 The combination has been granted fast track designation in this setting.11 Eganelisib has also received a fast track designation in combination with an immune checkpoint inhibitor and chemotherapy for frontline treatment of triple-negative breast cancer.39 The combination of eganelisib, atezolizumab (Tecentriq), and nab-paclitaxel (Abraxane) is being evaluated in the ongoing phase 2 MARIO-3 trial (NCT03961698). ■

For a full list of references, see the article at OncLive.com.
UKONIQ™
umbralisib 200 mg tablets

THE FIRST AND ONLY TARGETED KINASE INHIBITOR OF PI3K-DELTA AND CK1-_EPSILON

IMPORTANT SAFETY INFORMATION

Infections: Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade 3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for Pneumocystis jiroveci pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

Neutropenia: Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 10⁹/L (Grade 3-4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia.

Diarrhea or Non-Infectious Colitis: Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., >6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ.

Hepatotoxicity: Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

INDICATIONS

UKONIQ is indicated for the treatment of adult patients with:

- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen
- Relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy

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

Serious Cutaneous Reactions: Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ for severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade. Provide supportive care as appropriate.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5: UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons, particularly in patients who also have aspirin hypersensitivity.

Embryo-fetal Toxicity: Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose.

Serious adverse reactions occurred in 18% of 221 patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

The most common adverse reactions (>15%), including laboratory abnormalities, in 221 patients who received UKONIQ were increased creatinine (79%), diarrhea-colitis (58%), fatigue (41%), nausea (38%), neutropenia (33%), ALT increase (33%), AST increase (32%), musculoskeletal pain (27%), anemia (27%), thrombocytopenia (26%), upper respiratory tract infection (21%), vomiting (21%), abdominal pain (19%), decreased appetite (19%), and rash (18%).

Lactation: Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose.

Please see Brief Summary of the full Prescribing Information on the following pages.
UKONIQ™ (umbralisib) tablets, for oral use

1. Indications

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20 based regimen.

2. Dosage and Administration

See Dosage and Administration (2.2) for the recommended dosage of UKONIQ.

3. Adverse Reactions

The most common adverse reactions include:
- Diarrhea or non-infectious colitis
- Fatigue
- Nausea
- Vomiting
- Abdominal pain
- Upper respiratory tract infections

Other adverse reactions include:
- Myelosuppression
- Infections
- Gastrointestinal disorders
- Hypersensitivity reactions

4. Contraindications

UKONIQ is contraindicated in patients with a history of a severe hypersensitivity reaction to UKONIQ or any of the components of UKONIQ.

5. Warnings and Precautions

5.1. Infecions

Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in 3%. The most frequent grade 3 or 4 infections included pneumonia, sepsis, and urinary tract infection. The median time to onset of grade 2 or higher infection was 2.4 months (range: 0.1 to 21 months) (see Adverse Reactions (6.1)).

5.2. Neutropenia

Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 or higher neutropenia occurred in 10% of 335 patients, with fatal neutropenia occurring in 1%. The most frequent grade 3 or 4 neutropenia included pneumonia, sepsis, and urinary tract infection. The median time to onset of grade 2 or higher neutropenia was 2.4 months (range: 0.1 to 21 months) (see Adverse Reactions (6.1)).

5.3. Diarrhea or Non-infectious Colitis

Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Grade 3 or higher diarrhea or colitis occurred in 5% of 335 patients and Grade 4 diarrhea or colitis occurred in 3% (see Adverse Reactions (6.1)). The median duration of Grade 3 or 4 diarrhea or colitis was 1 month (range: 1 to 23 months), with 75% of cases occurring by 2.9 months.

For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline for 2 or more days), perform stool blood test for occult blood, change in bowel habits, or perineal signs, withhold UKONIQ until resolved and provide supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia (see Dosage and Administration (2.2)).

5.4. Myelosuppression

Serious myelosuppression occurred in patients treated with UKONIQ. Grade 3 or 4 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9% (see Adverse Reactions (6.1)). The median time to onset of Grade 3 or 4 neutropenia was 45 days. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil counts < 1 x 10^9/L. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia (see Dosage and Administration (2.2)).

5.5. Severe Cutaneous Reactions

Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular) (see Adverse Reactions (6.1)). The median time to onset of Grade 3 or higher cutaneous reaction was 15 days (range: 9 days to 6.4 months).

Monitor patients for new or worsening cutaneous reactions. Review all concurrent medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade (see Dosage and Administration (2.3)).

5.6. Allergic Reactions

UKONIQ, with its mechanism of PI3K inhibition, may cause severe cutaneous reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of severe cutaneous reactions (SJS, TEN, DRESS) is low, it is frequently seen in patients who also have aspirin hypersensitivity.

5.7. Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, treatment of umbilical cord blood from pregnant mice during the period of organogenesis caused certain developmental outcomes including embryofetal mortality and fetal malformations at maternal exposures comparable to those in patients at the recommended dose of 800 mg. 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 and for one month after the last dose (see Use in Specific Populations (8.1, 8.3)).

6. Adverse Reactions

The following are the most common adverse reactions:

- Diarrhea or non-infectious colitis
- Fatigue
- Nausea
- Vomiting
- Abdominal pain
- Upper respiratory tract infections

Other adverse reactions include:
- Myelosuppression
- Infections
- Gastrointestinal disorders
- Hypersensitivity reactions

7. Summary of Other Important Information

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least three prior lines of systemic therapy.

8. Use in Specific Populations

8.1. Pregnancy

Based on findings from animal studies and the mechanism of action (see Clinical Pharmacology (12.12)), UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of umbralisib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and structural abnormalities. Clinical recognition of pregnancies is 2% and 15% to 20%, respectively.

Data

Animal Data

An ex vivo feline development study in mice, pregnant animals
were administered oral doses of umbilasit at 100, 200, and 400 mg/day during the period of organogenesis. Malformations were observed at doses of 200 mg/kg/day (left palate and nasal raphe facial) in mice. Additional findings occurred starting at the dose of 100 mg/kg/day and included folded retina, delayed ossification of sternebrae and vertebrae, increased resorptions, and increased post-implantation loss. The exposure (AUC) at a dose of 100 mg/kg/day in mice is approximately equivalent to the human exposure at the recommended dose of 800 mg. In an embryo-fetal development study in rabbits, pregnant animals were administered oral doses of umbilasit at 30, 100, and 300 mg/kg/day during the period of organogenesis. Administration at 300 mg/kg/day resulted in maternal toxicity (decreased food consumption and body weight) and reduced fetal weights. The exposure (AUC) at 300 mg/kg/day in rabbits is approximately 0.03 times the exposure in human patients at the recommended dose of 800 mg.

8.2. Lactation

Risk Summary

There are no data on the presence of umbilasit in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions from umbilasit in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose.

8.3. Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

Advise female patients of reproductive potential to use highly effective contraception during treatment with UKONIQ and for at least 4 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose.

Infertility

Males

Based on the findings from mice and dogs, UKONIQ may impair male fertility [see Nonclinical Toxicology (13.1)]. Trend for reversibility was noted in dogs 30 days after the last dose.

8.4. Pediatric Use

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

8.5. Geriatric Use

Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, 56% of patients were 65 years of age or older, while 19% were 75 years of age and older. No overall differences in effectiveness or pharmacokinetics were observed between these patients and younger patients. In patients 65 years of age and older, 23% experienced serious adverse reactions compared to 12% in patients younger than 65 years of age. There was a higher incidence of infectious serious adverse reactions in patients 65 years of age or older (13%) compared to patients younger than 65 years of age (4%).

8.6. Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment [creatinine clearance (CLcr) ≥ 30 to < 90 mL/min estimated by Cockcroft-Gault equation] [see Clinical Pharmacology (12.3)]. UKONIQ has not been studied in patients with severe renal impairment (CLcr < 30 mL/min).

8.7. Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST ≤ ULN or total bilirubin > 1 to 1.5 × ULN and any AST) [see Clinical Pharmacology (12.3)]. UKONIQ has not been studied in patients with moderate (total bilirubin > 1.5 to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

14. CLINICAL STUDIES

14.1. Marginal Zone Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UX1701-205 (NCT02793583), an open-label, multi-center, multi-cohort trial. Patients with MZL were required to have received at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PK inhibitor. Patients received UKONIQ 0 mg orally once daily until disease progression or unacceptable toxicity. A total of 69 patients with MZ (extranodal (N=38), nodal (N=20), and splenic (N=11)) were enrolled in this cohort. The median age was 67 years (range: 34 to 88 years), 52% were female, 13% were White, 7% were Black, 3% were Asian, 7% were Other, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy. Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.3 months (range: 15.0 to 28.7 months). Efficacy results are shown in Table 5.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>34 (49)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.30, 0.61</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>23 (33)</td>
</tr>
</tbody>
</table>

Table 5: Efficacy Results in Patients with MZL (Study 205)

14.2. Follicular Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UX1701-205, an open-label, multi-center, multi-cohort trial (NCT02793583). Patients with relapsed or refractory FL were required to have received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3b FL, large cell transformation, prior alloengenic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received UKONIQ 0 mg orally once daily until disease progression or unacceptable toxicity. A total of 117 patients with FL were enrolled in this cohort. The median age was 65 years (range: 29 to 87 years), 38% were female, 80% were White, 4% were Black, 7.3% had Stage III-N disease, 38% had bulky disease, and 97% had a baseline ECOG performance status of 0 to 1. Patients had a median of 3 prior lines of therapy (range: 1 to 10), with 36% refractory to their last therapy. Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.1 months (range: 13.5 to 29.6 months). Efficacy results are shown in Table 6.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>50 (43)</td>
</tr>
<tr>
<td>95% CI</td>
<td>33.6, 52.2</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>46 (39)</td>
</tr>
</tbody>
</table>

Table 6: Efficacy Results in Patients With Relapsed or Refractory FL (Study 205)

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.7)]. Use in Specific Populations (8.1, 8.3). Adverse males of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose [see Use in Specific Populations (8.3)]. Advise males with female partners of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose [see Use in Specific Populations (8.3)].

Lactation

Advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose [see Use in Specific Populations (8.3)].

Infertility

Advise males of reproductive potential that UKONIQ may impair fertility [see Use in Specific Populations (8.3)].

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5

Advise patients that UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain susceptible persons [see Warnings and Precautions (5.6)].

Administration

Inform patients to take UKONIQ orally once daily at approximately the same time each day with food and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to crush, break, cut or chew tablets [see Dosage and Administration (2.1)].

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

Distributed by:
TG Therapeutics, Inc.
343 Thornall Street, Suite 740
Edison, NJ 08837

For patient information:
https://www.tgtherapeutics.com/our-products/patient/UKONIQ™ is a trademark of TG Therapeutics, Inc.
© TG Therapeutics, Inc. 2021
US-LUM 2000114
The highly heterogeneous nature of cholangiocarcinoma at the genomic, epigenetic, and molecular levels has led to the development of effective new treatments for patients with these rare malignant tumors. Cholangiocarcinoma, the second most common primary hepatic malignancy, often presents in advanced stages with reported 5-year survival outcomes of less than 10%.

For the past decade, investigators have leaned on targeted therapeutic approaches to better understand these tumors and have finally opened the door to a plethora of new agents, some of which are already helping to improve outcomes for certain patient subsets.

During a recent OncLive Peer Exchange®, a panel of gastrointestinal oncology experts discussed a variety of targetable genetic aberrations that have been observed in patients with cholangiocarcinoma. They also discussed several targeted treatments that are showing promise in patients with tumors that harbor such aberrations. These agents include FGFR inhibitors, the first of which was recently approved, and IDH inhibitors, with many others under active clinical investigation and expected to move into clinical practice in the coming years.

Identifying Targetable Genetic Aberrations

An increasing number of targets are being identified in cholangiocarcinoma. “I would say maybe up to 50% of [patients with] cholangiocarcinoma, particularly intrahepatic, may have an actionable or targetable therapy option,” R. Kate Kelley, MD, said. In patients with intrahepatic cholangiocarcinoma, IDH1 mutations and FGFR2 gene fusions have been the most frequent alterations identified. Less common targets include BRAF mutations, NTRK fusions, ROS1 fusions, and microsatellite instability-high (MSI-H) status, which Kelley said may also be observed in some patients with extrahepatic disease. Additionally, HER2 amplification or overexpression may also be present in some cases of extrahepatic disease.

“Those are the golden tickets we don’t want to miss,” she said.

Since targetable genetic aberrations are rare, some providers may experience “precision medicine frustration and fatigue” when testing for them, moderator John L. Marshall, MD, said. “A [small] return rate on a disease that you might only see 5 or 6 times a year may not feel worth it, but I think part of what we want to emphasize is the importance of doing this correctly using today’s standards, so if that golden ticket is actually sitting across from you in the exam room, you don’t miss it,” he explained.

The panelists proceeded to discuss which methods they use to assess for actionable targets. “We’ve evolved to using...”
next-generation sequencing [NGS], but not all next-generation sequencing is the same,” panelist Sameek Roychowdhury, MD, PhD, said. He explained that the NGS test used should include RNA sequencing, “RNA testing is particularly valuable for fusions. As long as you’re doing DNA and RNA testing, you’re likely to capture all these genes, mutations, amplifications, and gene fusions or rearrangements,” he said. If tissue-based NGS is not safe, feasible, or possible because of time constraints, Roychowdhury said liquid biopsy can be considered but noted that this modality is likely to miss 10% to 40% of gene fusions. “If it’s positive, it’s positive, and if it’s negative, I wouldn’t discount another gene being present.”

Because cholangiocarcinoma is such a heterogeneous cancer and targets are rapidly changing as the disease is becoming better understood, the panelists emphasized the importance of working with industry partners who have the most up-to-date platforms vs trying to handle testing internally.

Speaking from experience, Milind Javle, MD, said, “We had our own fantastic [internal assay] panel, but [we struggled to explain to] people that we were not going to send tissue there because it doesn’t check FGFR fusions. At this point, there are 150 fusions. The current platform that we have does detect fusions, but I think there’s variability...there should be some uniformity and certain standards, which I don’t believe there are at this point,” she said.

If feasible, it is important that molecular testing be conducted as early as possible. “I recommend earlier testing, especially for advanced or metastatic cholangiocarcinoma,” Roychowdhury said. “[When a diagnosis is first made], you could get a good tissue specimen and start gemcitabine/cisplatin, maybe consider a clinical trial, and do early testing so that you can start thinking about and have time to get those results.” He noted that this strategy helps give providers more breathing room to find solutions for addressing any targetable genetic findings, especially those that may not be standard of care yet. “Maybe you need to find that patient a clinical trial, or maybe you’re going to have to do some complicated paperwork to figure out how to get them an ERBB2 inhibitor, because [the agent] is not yet approved for that indication,” he explained.

**FGFR INHIBITORS**

The body of data on FGFR inhibitors is rapidly growing, Kelley said. She noted that the most data are currently available for activating FGFR2 fusions or rearrangements, which is the target of pemigatinib (Pemazyre), the first FDA-approved FGFR inhibitor for cholangiocarcinoma, and infigratinib, which was granted priority review by the FDA in December 2020. Both of these agents are ATP-competitive inhibitors. There has also been promising data around futibatinib, which is a non-ATP competitive covalent inhibitor that targets kinase in a different location and has shown activity in resistance, she said. Based on such findings, specifically the phase 2 FOENIX-CCA2 trial (NCT02052778), the FDA granted futibatinib breakthrough therapy designation on April 1, 2021, for patients with previously treated, locally advanced, or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including fusions.5

**Pemigatinib**

Pemigatinib was granted accelerated approval on April 17, 2020, along with the FoundationOne CDX as a companion diagnostic for patient selection. Approval was based on data from FIGHT-202 (NCT02924376), a multicenter, open-label, single-arm trial that included 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma that progressed after at least 1 prior therapy and had an FGFR2 gene fusion or rearrangement. “[Data from] FIGHT-202 showed durable and pretty deep responses, with the waterfall plot showing a pretty substantial regression in almost all patients. With this drug, the uniformity of the regressions and the durability led to an accelerated FDA approval, even in the absence of a randomized trial,” Kelley said.

After a median follow-up of 17.8 months, the overall response rate (ORR) was 36%, which included 3 complete responses (CRs) and 35 partial responses (PRs). The median duration of response (DOR) was 9.1 months with responses lasting at least 6 months in 24 of the 38 (63%) responders and at least 12 months in 7 (18%) responders. The most common adverse effect (AE) across grades was hyperphosphatemia (60%). In February 2021, the label for pemigatinib was updated to include a warning and a recommended dosage of 9 mg orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles for patients with severe hepatic impairment, defined as total bilirubin greater than 3 × upper limit of normal with any aspartate aminotransferase.

Pemigatinib is currently being studied in FIGHT-302 (NCT03656536), a phase 3 trial comparing pemigatinib with gemcitabine plus cisplatin in treatment-naive patients with advanced cholangiocarcinoma harboring FGFR2 rearrangements.6 The study plans to enroll more than 400 patients globally and is currently recruiting patients.

**Infigratinib**

Infigratinib has shown comparable results to pemigatinib, Kelley said. Like pemigatinib, it was studied in a single-arm, phase 2 study (NCT02150967). The study included 108 patients with FGFR2 gene fusions or rearrangements, 54% of who had received at least 2 prior treatments. After a median follow-up of 10.6 months, the ORR was 23.1% and included 1 CR and 24 PRs. The median DOR was 5 months (range, 0.9-19.1). Among the responders, 32% had a DOR lasting at least 6 months. The median progression-free survival (PFS) was 7.3 months (95% CI, 5.6-7.6). In a subset analysis, the ORR for those receiving infigratinib in the second-line setting was 34%. For those receiving it in the third and later lines the ORR was 13.8%.

The AE profile of infigratinib was comparable to that of pemigatinib. The most common treatment-emergent AEs included hyperphosphatemia (76.9%); eye disorders, excluding central serous retinopathy (CSR) and retinal pigment epithelial detachment (RPED; 67.6%); stomatitis (54.6%); and fatigue (39.8%). CSR/RPED was observed in 16.7% of patients, including 1 who experienced an AE that was grade 3. Other common grade 3/4 AEs included stomatitis (14.8%), hyponatremia (13.0%), and hypophosphatemia (13.0%), all...
of which were grade 3 except 1 case of hypophosphatemia.

Although infigratinib and pemigatinib are both ATP-competitive inhibitors, Javle noted some differences between them. “Infigratinib is an ATP-competitive inhibitor very specific for FGFR1, FGFR2, and FGFR3. It has much less FGFR4 activity compared with some of the other agents, such as pemigatinib and futibatinib, and it’s very potent for FGFR2,” he said.

Investigators are evaluating infigratinib in the phase 3 PROOF 301 trial (NCT03773302), which is comparing the agent with gemcitabine plus cisplatin in treatment-naïve patients with advanced cholangiocarcinoma harboring FGFR2 gene fusions or translocations.10 Whereas the FIGHT-302 trial uses 1:1 randomization to pemigatinib or gemcitabine plus placebo, the PROOF 301 trial will have 2:1 randomization to infigratinib or gemcitabine plus placebo.8,10

**Futibatinib**

At the time of the Peer Exchange, data for futibatinib were not reported and the panelists were very hopeful about the drug’s prospects. Whereas the ultimate hope with pemigatinib and infigratinib is that they will enable a chemotherapy-free, targeted therapy option in the front line, along with any subsequent-line indications, another hope is that futibatinib will provide a powerful second- and subsequent-line option for patients, including those previously treated with pemigatinib or infigratinib who may have acquired a resistance mutation, Kelley said. “The wave of the future may be nuancing this pathway and learning how to inhibit it sequentially like we have in EGFR-mutated lung cancer or ALK-fusion lung cancer. FGFR is a huge space,” she said.

Recently, Taiho Oncology, the manufacturer of futibatinib, presented the safety and efficacy results from the phase 2, single-arm FOENIX-CCA2 trial, which evaluated futibatinib in 103 patients with intrahepatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions, who progressed after at least 1 line of therapy.11 The ORR was 41.7% (95% CI, 32.1%-51.9%) and responses were durable, with a median DOR of 9.7 months (95% CI, 7.6-17.0). Among responders, 72% maintained their responses at least 6 months and 14% maintained a response of at least 12 months. The median PFS was 9.0 months (95% CI, 6.9-13.1). The overall survival data (OS) at the time of presentation was immature and ongoing with investigators reporting median OS of 21.7 months (95% CI, 14.5-not reached), with 72% of patients alive at 12 months.

Treatment-related AEs were similar to those observed with pemigatinib and infigratinib, with hyperphosphatemia (85%), alopecia (33%), and dry mouth (30%) being most common.11 The most frequent grade 3 AE was hyperphosphatemia (30%), which resolved with adequate management. One case of grade 4 increase in serum alanine aminotransferase was observed, but there were no treatment-related deaths.

**Dealing With FGFR Inhibitor-Related AEs**

With one FGFR inhibitor already FDA-approved and other approvals anticipated, Javle noted that while these agents have general systemic AEs, such as alopecia, nail changes, mucositis, and arthralgia. Other AEs may require special consideration before use. These include mechanism-related AEs, particularly hyperphosphatemia, and bodily changes, such as the ocular AEs, which he said are the most important to watch out for. “[Ocular monitoring] is not usually in the armamentarium of investigations, such as ophthalmological examination every 2 or 3 months, along with OCT [optical coherence tomography]. We have learned to do that,” he said.

As for hyperphosphatemia, which occurs less commonly than hyperphosphatemia, Javle said a patient’s serum phosphorous levels should be periodically measured and the condition can usually be managed with “dietary restriction of phosphates as a first step, [adding] a chelating agent as a second step, and then dose reduction as a third step.” He noted that although none has been observed, an important question is whether this AE has any clinical consequences.

Kelley said hyperphosphatemia is more concerning as it is associated with a risk of ectopic calcification and affects approximately 70% of patients. “Most patients on these drugs end up taking a binder such as sevelamer [Renvela, Renagel] which we would use [for] a patient with chronic kidney disease,” she said, noting these agents are not given as prophylaxis but when serum phosphorous levels are found to be elevated.

**IDH1 INHIBITION**

IDH1 inhibitors are not fundamentally cytotoxic and work through a completely different mechanism from most cancer treatments, Kelley said. She explained that the IDH1 gene, particularly **IDH1**, causes the oncometabolite 2-hydroxyglutarate to accumulate downstream in the cell microenvironment, causing a differentiation block that leads to a proliferation of immature cells and subsequent oncogenesis. IDH1 inhibitors attempt to reestablish normal differentiation. “Approximately 15% of [patients with] intrahepatic cholangiocarcinomas have an IDH1 mutation. We think this is also a distinct clinical phenotype, just like FGFR,” Kelley said.

An IDH1 inhibitor showing promise in cholangiocarcinoma is ivosidenib (Tibsovo),

---

**Fast Facts**

**Targeted Treatment Landscape for Patients with Cholangiocarcinoma**

Molecular profiling of cancer tumor tissue is highly recommended as it may direct patients toward more effective, personalized treatment options.

Clinical research has shown that up to 50% of patients with cholangiocarcinoma have current druggable mutations, amplifications or fusions including:

- **IDH1, IDH2, BRAF, FGFR, HER2, PIK3CA, MET, and others**

Phase 3 trials with IDH1/IDH2 or FGFR inhibitors as first- and/or second-line treatment are ongoing

**Approved agents:**

- Futibatinib (FGFR inhibitor): granted breakthrough therapy designation in April 2021
- Ivosidenib (IDH1 inhibitor): new drug application filed for FDA review in March 2021
- Infigratinib (FGFR inhibitor): granted priority review in December 2020

---

**Agents under investigation:**

- Futibatinib (FGFR inhibitor): granted breakthrough therapy designation in April 2021
- Ivosidenib (IDH1 inhibitor): new drug application filed for FDA review in March 2021
- Infigratinib (FGFR inhibitor): granted priority review in December 2020
an agent approved for patients with acute myeloid leukemia (AML). While this agent has not shown dramatic response rates, it has been associated with improved PFS in data from the phase 3 ClarIDHy trial (NCT02989857). The median PFS for patients treated with ivosidenib (n = 124) was 2.7 months (95% CI, 1.6-4.2) vs 1.4 months (95% CI, 1.4-1.6) for those who received placebo (n = 61; HR, 0.37; 95% CI, 0.25-0.54; one-sided P = .0001).  

Although these numbers appear low, Kelley explained that there are some challenges with interpreting the data, such as the heterogeneity of the second- and third-line patients included. Nevertheless, the hazard ratio was significant. “There’s a distinct tail of the curve. We think this is a statistically positive trial, and although the absolute numbers are low, there’s a subset of patients who seem to be deriving a benefit,” she said.

Overall, ivosidenib was well tolerated, with ascites being the most common grade 3 or worse AE, affecting 7% of patients in the placebo and ivosidenib cohorts. Based on the safety and efficacy findings, on March 1, 2021, the drug’s manufacturer, Agios Pharmaceuticals, submitted a new drug application to the FDA requesting priority review of ivosidenib as a potential treatment for patients with previously treated IDH1-mutated cholangiocarcinoma.  

A REASON FOR HOPE 

The panelists said they were hopeful about the evolving treatment landscape for advanced cholangiocarcinoma. “I see futures in so many of these heterogeneous subsets; they will start classifying and nuanced themselves, whether it’s FGFR2, IDHI, or MSI-high, and as we go, we’ll discover more,” Kelley said, noting that these distinctions will enable providers to “finesse and tailor treatments to the individual patient’s tumor.”

Roychowdhury explained that while cholangiocarcinoma can lead to thoughts of poor survival and feelings of pessimism, the opportunities to improve care and outcomes are growing. “There is hope, and there are good therapies. Whether it’s standard therapies or clinical trials, we’ve got great options for these patients. Don’t be afraid of this disease. Don’t give up,” he said.

REFERENCES 

NOW APPROVED

FIND OUT MORE AT
PEPAXTOHCP.COM