GI Cancer Expert Is Searching for Big Leaps in Care

PEER EXCHANGE
Fresh Strategies Emerge in Early-Stage HER2+ BREAST CANCER

A New Crop of ER-Targeting Agents Takes Root

2021 GENITOURINARY CANCERS SYMPOSIUM
Findings Signal Progress in Urothelial Carcinoma

CLINICAL PERSPECTIVES
Anti-HER3 Agent Shows Promise in LUNG CANCER

Navitoclax Data Are Encouraging in MYELOFIBROSIS

CARBONE CANCER CENTER
Surgical Intervention Provides the Foundation for Exploring Immunotherapy in Glioblastoma

BY MAHUA DEY, MD
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-ITD-TKD mutation status.

MEC: mitoxantrone 8 mg/m², etoposide 100 mg/m², and cytarabine 1000 mg/m² once daily by IV infusion Days 1 to 5.

§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.

llLDAC: cytarabine 20 mg twice daily by SC injection or IV infusion for 10 days.

P vs salvage chemotherapy (n=124)

References:
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
Differential 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 hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia 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/arthralgia (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 their 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.

DOSE 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.

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, prior to the initiation of XOSPATA, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. 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 dosing or reduce dose for toxicities.

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, 3% 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. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of XOSPATA. 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)

Of 319 patients treated with XOSPATA in the clinical trials, 1% 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). 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 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

Pancratitis

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 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 (26%), eye disorders (25%), headache (24%), dizziness (22%), hypertension (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...
(12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

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%).

*Grouped terms: cardiac failure (cardiac failure, cardiac failure congestive, cardiomegaly, cardiomyopathy, chronic left ventricular failure, and ejection fraction decreased), hypersensitivity (anaphylactic reaction, angioedema, dermatitis allergic, drug hypersensitivity, erythema multiforme, hypersensitivity, and urticaria), pancreatitis (amylase increased, lipase increased, pancreatitis, pancreatitis acute), pericarditis/myocarditis (myocarditis, pericardial hemorrhage, pericardial rub, and pericarditis).

DRUG INTERACTIONS

Combined P-gp and Strong CYP3A Inducers
Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases gilteritinib 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 gilteritinib 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 gilteritinib 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 their use is considered essential for the care of the patient.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings from animal studies and its mechanism of action, XOSPATA can cause fetal harm when administered to a pregnant woman. There are no available data on XOSPATA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC24) approximately 0.4 times the AUC24 in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data
In an embryo-fetal development study in rats, pregnant animals received oral doses of gilteritinib of 0, 0.3, 3, 10, and 30 mg/kg/day during the period of organogenesis. Maternal findings at 30 mg/kg/day (resulting in exposures approximately 0.4 times the AUC24 in patients receiving the recommended dose) included decreased body weight and food consumption. Administration of gilteritinib at the dose of 30 mg/kg/day also resulted in embryo-fetal death (post implantation loss), decreased fetal body and placental weight, and decreased numbers of ossified sternebrae and sacral and caudal vertebrae, and increased incidence of fetal gross external (anasarca, local edema, exencephaly, cleft lip, cleft palate, short tail, and umbilical hernia), visceral (microphthalmia, atrial and/or ventricular defects, and malformed/absent kidney, and malpositioned adrenal, and ovary), and skeletal (sternoschisis, absent rib, fused rib, fused cervical arch, misaligned cervical vertebra, and absent thoracic vertebra) abnormalities.

Single oral administration of [14C] gilteritinib to pregnant rats resulted in transfer of radioactivity to the fetus similar to that observed in maternal plasma on day 14 of gestation. In addition, distribution profiles of radioactivity in most maternal tissues and the fetus on day 18 of gestation were similar to that on day 14 of gestation.

Lactation

Risk Summary
There are no data on the presence of gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Following administration of radiolabeled gilteritinib to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4 and 24 hours post-dose. In animal studies, gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

Females and Males of Reproductive Potential

Pregnancy testing
Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating XOSPATA treatment.

Contraception

Females
Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of XOSPATA.

Males
Advise males of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA.

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

Geriatric Use
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.

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Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 58.
by JASON HARRIS

Although targeted therapies are being developed for patients with gastrointestinal (GI) malignancies, John L. Marshall, MD, believes more extensive use of molecular profiling along with artificial intelligence algorithms will help unlock additional treatment options.
Patients Need a Bigger Voice

THE DAYS WHEN PATIENTS with cancer were kept in the dark about their diagnosis and treatment are long gone. However, despite the progress that has been made in integrating patients into the decision-making process, the oncology community still has a way to go to bridge the communications gap.

Patients’ perspective on their own care is very much on the minds of 2 of the leading oncologists whose views we capture in this issue of OncologyLive®: John L. Marshall, MD, and Maurie Markman, MD.

Marshall discusses some of the insights he gained into patients’ experiences after his wife, Liza, received a diagnosis of advanced triple-negative breast cancer. The couple has written a memoir, Off Our Chests: A Candid Tour Through the World of Cancer, that describes how they coped during her cancer journey. In the book, Marshall says he became “a born-again symptom management guy” after seeing his wife experience adverse effects of treatment. The Georgetown University gastrointestinal cancer specialist became more sensitive to his patients’ concerns.

Spending time on the patient’s side of the clinical equation also made Marshall realize that health care providers often fall short of the goal of shared decision-making. Although oncologists are talking to their patients, “they’re not understanding anything we’re saying,” Marshall said in an interview. “Their brains are over here thinking about something else. And we think, ‘OK, we’ve checked that box, [now let’s] check that box.’ But having participated in that on a bunch of levels, I realized just how far and how often we fail on that, and I’m hoping we can do a better job in closing that gap.”

Markman, the editor in chief of OncologyLive® and a 2018 Giants of Cancer Care® award winner in Gynecological Cancer, voices concern about whether those in the field adequately consider patients’ views when defining value in cancer care. Clinical experts and policy makers may frame the value of a given treatment approach, but patients may view the matter differently. “How much do we really know about the actual perceptions of individuals with cancer and other serious medical conditions concerning their own wishes regarding care and meaningful outcomes?” Markman asks in his column.

These provocative questions, posed by thoughtful oncologists, are worth pondering at a time when information is so readily accessible but so easily misunderstood. The OncLive® editorial team is interested in fostering this conversation. Please let our editorial director Gina Mauro know your thoughts at GMauro@Onclive.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION.  

Approved across 5 indications spanning a wide range of multiple myeloma patients

INDICATIONS
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:
• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
• as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.
Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.
Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 47 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
DARZALEX™: For a strong start to their treatment journey

~3 to 5 minute administration
- Subcutaneous injection is substantially faster than intravenous daratumumab1,2

The recommended dose of DARZALEX FASPRO™ is 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously over ~3 to 5 minutes. DARZALEX FASPRO™ is for subcutaneous use only. Do not administer intravenously.

See the Dosage and Administration section of the Prescribing Information for dosing considerations and dosing schedules for approved regimens.

See Important Safety Information below for hypersensitivity and administration reactions, pre-medication and post-medication requirements, and other important considerations for use of DARZALEX FASPRO™.

Efficacy consistent with intravenous daratumumab
- DARZALEX FASPRO™ demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients1
  - ORR was 41% (95% CI: 35%, 47%) for DARZALEX FASPRO™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259)
  - Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent

- In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with lenalidomide and dexamethasone (Drd) was evaluated in 65 patients with multiple myeloma who had received ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%)1

- In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%)1

Fewer systemic ARRs vs intravenous daratumumab
- Nearly 3x reduction in systemic administration-related reactions (ARRs) with DARZALEX FASPRO™ vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZALEX FASPRO™ had a systemic ARR of any grade vs 34% with intravenous daratumumab)1,3

- Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™. See Important Safety Information for more details1

Neutropenia
Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO™ until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO™, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia
Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of platelets.

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO™ can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO™ and for 3 months after the last dose.

The combination of DARZALEX FASPRO™ with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

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

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

ADVERSE REACTIONS
The most common adverse reaction (≥20%) with DARZALEX FASPRO™ monotherapy is: upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematologic laboratory abnormalities (≥40%) with DARZALEX FASPRO™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.


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Daratumumab may increase neutropenia induced by background therapy; consider symptomatic management. Administration of DARZALEX FASPRO. Monitor for local reactions and injection-site reaction was injection-site erythema. These local reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) administration-related reactions especially following the first and second injections. For anaphylactic reaction information.

Embryo-Fetal Toxicity

Daratumumab is a human IgG kappa monoclonal antibody that can be detected in the formulation [see Warnings and Precautions and Adverse Reactions].

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [see References]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions].

In combination with bortezomib, melphalan and prednisone the safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from week 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 8 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fatal adverse reactions occurred in 3.9% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dose interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain. Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>39 0</td>
<td></td>
</tr>
<tr>
<td>Bronchitisa</td>
<td>16 0</td>
<td></td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>15 7%</td>
<td></td>
</tr>
</tbody>
</table>

*Adverse reactions are described elsewhere in the labeling:
• Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
• Neutropenia [see Warning and Precautions].
• Thrombocytopenia [see Warning and Precautions].

Clinical Trials Experience

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

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from week 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 8 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fatal adverse reactions occurred in 3.9% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dose interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain. Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>39 0</td>
<td></td>
</tr>
<tr>
<td>Bronchitisa</td>
<td>16 0</td>
<td></td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>15 7%</td>
<td></td>
</tr>
</tbody>
</table>

*Adverse reactions are described elsewhere in the labeling:
• Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
• Neutropenia [see Warning and Precautions].
• Thrombocytopenia [see Warning and Precautions].

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

**Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (continued)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>34</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

- **Upper respiratory tract infection** includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.
- **Pneumonia** includes lower respiratory tract infection, lung infection, pneumonia, and pneumonia bacterial.
- Abdominal pain includes abdominal pain, and abdominal pain upper.
- **Fatigue** includes asthenia, and fatigue.
- Edema peripheral includes edema, edema peripheral, and peripheral swelling.
- Cough includes cough, and productive cough.
- Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) include:

- **General disorders and administration site conditions:** infusion reaction, injection site reaction, chills
- Infections: herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** headache, paresthesia
- **Metabolism and nutrition disorders:** hyponatremia, hyperglycemia
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, pulmonary edema
- **Cardiac disorders:** atrial fibrillation

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

**Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Denominator is based on the safety population treated with D-VMP (N=67).

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

**Relapsed/Refractory Multiple Myeloma**

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 3 summarizes the adverse reactions in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

**Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

- **Fatigue** includes asthenia, and fatigue.
- **Upper respiratory tract infection** includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
- **Pneumonia** includes lower respiratory tract infection, lung infection, and pneumonia.
- **Bronchitis** includes bronchitis, and bronchitis viral.
- **Dyspnea** includes dyspnea, and dyspnea exertional.
- **Cough** includes cough, and productive cough.
- Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) include:

- Fever
- Hypertension
- Hypoglycemia
- Diarrhea
- Influenza
- Anemia
- Upper respiratory tract infection
- Nasopharyngitis
- Headache
- Back pain
- Peripheral sensory neuropathy
- Bronchitis
- Cough
- Fatigue
- Peripheral edema
- Abdominal pain
- Myalgia
- Arthralgia
- Rash
- Urinary tract infection
- Vomiting
- Hemoptysis
- Nausea
- Pruritus
- Dyspnea
- Hyperglycemia
- Hypocalcemia
- Paresthesia
- Arm swelling
- Lower respiratory tract infection
- Rhinitis
- Sinusitis
- Infection
- Pharyngitis
- Rash
Patients received [see Clinical Trials (14.2) in Full Prescribing Information]. The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA Monotherapy a Denominator is based on the safety population treated with D-Rd (N=65).

DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

• General disorders and administration site conditions: chills, infusion reaction, injection site reaction
• Vascular disorders: hypertension, hypertension

Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

### Table 4: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with D-Rd (N=65).

### Monotherapy

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or Intravenous Daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks from week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

### Table 5: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=258)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24</td>
<td>1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>general disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infusion reactions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>13</td>
<td>2&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9</td>
<td>1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;f&lt;/sup&gt;</td>
<td>6</td>
<td>1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sin支炎, and upper respiratory tract infection.

<sup>b</sup> Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jiroveci pneumonia, and pneumonia.

<sup>c</sup> Fatigue includes asthenia, and fatigue.

<sup>d</sup> Infusion reactions includes terms determined by investigators to be related to infusion.

<sup>e</sup> Cough includes cough, and productive cough.

<sup>f</sup> Dyspnea includes dyspnea, and dyspnea exertional.

<sup>+</sup> Only grade 3 adverse reactions occurred.

Grade 5 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO include:

• General disorders and administration site conditions: injection site reaction, peripheral edema
• Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, muscle spasms
• Gastrointestinal disorders: constipation, vomiting, abdominal pain, nausea
• Metabolism and nutrition disorders: decreased appetite, hyperglycemia, hypocalcemia, dehydration
• Psychiatric disorders: insomnia
• Vascular disorders: hypertension, hypotension
• Nervous system disorders: dizziness, peripheral sensory neuropathy, paresthesia
• Infections: bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B reactivation
• Skin and subcutaneous tissue disorders: pruritus, rash
• Cardiac disorders: atrial fibrillation
• Respiratory, thoracic and mediastinal disorders: pulmonary edema

### Table 6: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intravenous Daratumumab&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>decreased leukocytes</td>
<td>65</td>
<td>19</td>
</tr>
<tr>
<td>decreased lymphocytes</td>
<td>59</td>
<td>36</td>
</tr>
<tr>
<td>decreased neutrophils</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>decreased platelets</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>decreased hemoglobin</td>
<td>42</td>
<td>14</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

### Immunogenicity

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

Treatment-emergent anti-daratumumab antibodies were tested in 451 patients treated with DARZALEX FASPRO as monotherapy or as part of a combination therapy. One patient (0.2%) who received DARZALEX FASPRO tested positive for anti-daratumumab antibodies and transient neutralizing antibodies. However, the incidence of antibody development might not have been reliably determined because the assays that were used have limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab.

Treatment-emergent anti-rHuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (16/192) of patients who received DARZALEX FASPRO as part of combination therapy. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposures. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

### Postmarketing Experience

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

**Immune System:** Anaphylactic reaction
**Gastrointestinal:** Pancreatitis
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiotreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products intercedes in the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse neonatal or fetal outcomes. Animal reproduction studies have not been conducted.

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

The combination of DARZALEX FASPRO and lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Lenalidomide is only available through a REMS program. Refer to the lenalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defers administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 6 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during pregnancy with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO.

Refer to lenalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during pregnancy with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

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

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, refer to the lenalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness were observed based on age. Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥75 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥75 years of age included pneumonia.

Clinical studies of DARZALEX FASPRO as part of a combination therapy did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hepatitis B Virus (HBV) Reactivation

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing (see Warnings and Precautions).

Neutropenia

Advise patients to contact their healthcare provider if they have a fever (see Warnings and Precautions).

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding (see Warnings and Precautions).

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to discuss their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, Use in Specific Populations).

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for at least 3 months after the last dose (see Use in Specific Populations).

Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide is only available through a REMS program (see Use in Specific Populations).

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion (see Warnings and Precautions).

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

Hepatitis B Virus (HBV) Reactivation

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

Product of Switzerland

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Horsham, PA 19044
U.S. License Number 1984

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Patient Perspective Should Be Part of Assessing Value in Cancer Care

by MAURIE MARKMAN, MD

THE FINANCIAL IMPACT OF a cancer diagnosis on patients and their families is increasingly recognized as a serious and worsening societal concern. Costs associated with anticancer therapeutics continue to rise, although it also is recognized that the overall effectiveness of therapy has improved.

The relationship between the benefits of care versus the cost of specific interventions (including the administration of pharmaceutical agents) has been a raging debate within the health care community for decades. The urgency associated with the question has only increased in recent years with the rapid acceleration in the development of novel approaches for managing multiple serious medical conditions.

No area of medicine has been more affected than oncology by the striking success of innovation such as new drugs and devices that improve the quantity and quality of life, which essentially has developed in the absence of a coherent strategy to control the rapid rise in the cost of care. This rapid rise has occurred despite the concerted efforts of governmental and private payers and employers. Over the past several years, a number of organizations and academics have advanced their opinions about this societal dilemma. These efforts include attempts to define the “value” of a specific intervention, and, notably, to declare that a particular intervention or drug may not provide sufficient value to justify its use in routine (noninvestigative) oncology care.

This commentary highlights the question of how value in cancer care will be determined in the future and specifically acknowledges the critical difference between the population versus the individual when considering these issues. Samuel Hellman, MD, a noted radiation oncologist and a 2016 Giants of Cancer Care® award winner, eloquently articulated the matter in his provocative 2014 essay published in the Journal of Clinical Oncology:

“The utilitarian [approach] is clearly appropriate to public health considerations, but what is learned for public health may not necessarily be in the best interest of an individual patient….Too often we assume that survival or cure is a sufficient metric, with no similar quantitative measure of other factors. This often leads to the so-called best treatment being not what the patient wants. All personal care requires consideration of both the helpful and harmful consequences of treatment in the context of individual patient comorbidity, preferences, and fears.”

This commentary can only begin to scratch the surface of the critical questions posed by Dr Hellman. How much do we really know about the wishes of individuals with cancer and other serious medical conditions regarding their care and their perceptions of meaningful outcomes, as opposed to what clinical investigators, academic leaders, and health policy experts have suggested, or at times proclaimed, in peer-reviewed publications as being the most relevant? Below are several examples to consider.

STUDIES RAISE QUESTIONS

In a survey of 1090 patients with breast and non–small cell lung cancer, physicians and patients who were asked to rate the severity of adverse effects experienced under-reporting by physicians that ranged from 40.7% to 74.7%, and the most serious adverse effects as noted by patients were underreported by physicians from 13.0% to 50.0%.

This degree of discordance between what oncologists claim to have measured and what patients report they actually experienced raises a concern about the reliability of published clinical trial assessments for providing a meaningful assessment at the individual patient level of the risk-to-benefit ratio associated with study regimens.

In a survey of 374 women treated for breast cancer, investigators found that the patients’ perception of the quality of their care was strongly related to the “process...
of getting care” rather than a measure of the specific medical interventions delivered. Therefore, how patients with cancer feel they are being treated by their clinical team may be as important—if not more important—as the regimens they receive.

Several recently reported studies have noted the frequent use in breast cancer (early stage or advanced/metastatic disease) of tumor markers or imaging techniques where there was limited or no evidence that such testing improves clinical outcomes, particularly in individuals at low risk of progression or where there was no evidence of involvement of the organ being examined (eg, central nervous system screening in the absence of neurologic symptoms). The studies’ authors highlight the need for future investigation to understand the reasons for widespread use of these strategies. Of note, there is the reassurance “value” that testing may provide a patient when a negative test result is obtained. How does one calculate the emotional versus financial cost benefit associated with such individual reassurance?

The final example relates to the fundamental goals of therapy and the primary outcomes of anticancer drug therapy studies. The industry gold standard is a statistically significant improvement in overall survival in an appropriately powered randomized phase 3 trial. However, in a provocative detailed interview with 22 survivors of ovarian cancer, the respondents challenged this assertion, suggesting instead that “they preferred an individualized approach to care focusing on quality of life.”

Clearly, there is much to learn through a far more expansive exploration of “value,” as defined by the patient with cancer, that hopefully will take place in the future.

REFERENCES
Melphalan Flufenamide Is Approved for RRMM

The FDA has granted accelerated approval to the peptide-drug conjugate melphalan flufenamide (Pepaxto) for use in combination with dexamethasone in adult patients with relapsed or refractory multiple myeloma (RRMM), who have received at least 4 prior lines of therapy and whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 CD38-directed monoclonal antibody.

The decision was based on efficacy data of a subpopulation of patients from the single-arm, phase 2 HORIZON study (NCT02963493). Investigators evaluated 97 patients. The overall response rate was 23.7% (95% CI, 15.7%-33.4%), and the median duration of response was 4.2 months.

Of note, the FDA specified that the safety and efficacy of melphalan flufenamide has not been established for use as a conditioning regimen in patients receiving transplants and is not recommended as such outside controlled clinical trials.

TO READ MORE, VISIT bit.ly/3kFccVZ.

Cemiplimab Gets Green Light in NSCLC

The FDA has approved cemiplimab-rwlc (Libtayo) for use in the frontline treatment of patients with advanced non–small cell lung cancer (NSCLC) with a PD-L1 expression level of 50% or higher and no EGFR, ALK, or ROS1 aberrations.

Findings from the phase 3 EMPOWER-Lung 1 trial (NCT03088540) evaluating cemiplimab compared with investigator’s choice of platinum-doublet chemotherapy provided the basis for the approval. The median overall survival was 22.1 months (95% CI, 17.7-not evaluable) for patients in the cemiplimab arm (n = 356) compared with 14.3 months (95% CI, 11.7-19.2) in the chemotherapy arm (n = 354; HR, 0.68; 95% CI, 0.53-0.87; P = .0022).

The median progression-free survival in the investigational arm was 6.2 months (95% CI, 4.5-8.3) versus 5.6 months (95% CI, 4.5-6.1) in the control arm (HR, 0.59; 95% CI, 0.49-0.72; P < .0001). The confirmed overall response rates per blinded independent review committee were 37% (95% CI, 32%-42%) and 21% (95% CI, 17%-25%), respectively.

Additionally, the FDA approved the PD-L1 IHC 22C3 pharmDx assay for expanded use in patients with NSCLC based on data from EMPOWER-Lung 1.

TO READ MORE, VISIT bit.ly/2PlykJd, bit.ly/3e728DK.

First-in-Class Therapy Arrives for Prevention of Chemotherapy-Related AE

The FDA has approved the CDK4/6 inhibitor trilaciclib (Cosela) as the first therapy in its class to reduce the frequency of chemotherapy-induced bone marrow suppression in adults receiving certain types of chemotherapy for extensive-stage small cell lung cancer (ES-SCLC).

The efficacy data to support the approval was from a pooled analysis of 123 patients who received trilaciclib prior to chemotherapy and 119 patients who received placebo from 3 phase 2 trials of adult patients with ES-SCLC: G1T28-02 (NCT02499770), G1T28-05 (NCT03041311), and G1T28-03 (NCT02514447). Results showed that tumor responses were comparable between the treatment groups; 49.1% of patients who received trilaciclib experienced a response versus 51.8% of those given placebo (P = .7879). Patients in the experimental arm had a progression-free survival of 5.3 months (95% CI, 4.6-6.1) compared with 5.0 months for those in the placebo arm (HR, 0.80; 95% CI, 0.61-1.06; P = .1404). Additionally, the median overall survival was 10.6 months in both groups (HR, 1.00; 95% CI, 0.75-1.35; P = .8136).

TO READ MORE, VISIT bit.ly/3BWg1SF.

Lorlatinib Gets Expanded Approval for NSCLC

The FDA has granted regular approval to lorlatinib (Lorbrena) for patients with ALK-positive metastatic non–small cell lung cancer (NSCLC) as detected by an FDA-approved test.

The decision was based on findings from the pivotal phase 3 CROWN trial (NCT03052608), which evaluated 296 patients with previously untreated advanced ALK-positive NSCLC who were randomized 1:1 to receive either lorlatinib (n = 149) or crizotinib (Xalkori; n = 147).

Lorlatinib resulted in a 72% reduction in the risk of progression or death compared with crizotinib in treatment-naïve patients (HR, 0.28; 95% CI, 0.19-0.41; P < .0001) per blinded independent central review assessment. Results from a prespecified exploratory analysis demonstrated that among these patients, the intracranial objective response rate was 82% (95% CI, 57%-96%) in the lorlatinib arm versus 23% (95% CI, 5%-54%) in the crizotinib arm. Moreover, the intracranial duration of response was 12 months or longer in 79% of those who received lorlatinib (n = 11) versus 0% in those given crizotinib.

In 2018, the FDA granted accelerated approval to the agent for patients with ALK-positive metastatic NSCLC who had progressed on crizotinib and at least 1 other ALK inhibitor for metastatic disease, or who had disease that progressed on alectinib (Alecsensa) or ceritinib (Zykadia) as the first ALK inhibitor therapy for metastatic disease.

TO READ MORE, VISIT bit.ly/38bfFa5.

Pembrolizumab Loses SCLC Indication

Merck has voluntarily decided to withdraw the indication for pembrolizumab (Keytruda) from the US market for the treatment of patients with metastatic small cell lung cancer (SCLC) who experienced disease progression on or after platinum-based chemotherapy and at least 1 other line of treatment.

This action was done in accordance with the FDA’s standard procedures for assessing accelerated approvals that have not met their postmarketing requirements and as part of a broader industry-wide evaluation. The decision does not affect pembrolizumab’s other indications.

Pembrolizumab initially gained an approval in the SCLC setting in June 2019 based on overall response rates from 2 nonrandomized trials. Results from the phase 3 confirmatory KEYNOTE-604 trial (NCT03066778), which enrolled 453 patients, indicated that the addition of pembrolizumab to etoposide and carboplatin or cisplatin (EP) resulted in a significant improvement in median progression-free survival compared with placebo/EP (HR, 0.75; 95% CI, 0.61-0.91; P = .0023).

However, although the HR for overall survival (OS) favored pembrolizumab/EP, the significance threshold was missed (HR, 0.80; 95% CI, 0.64-0.98; P = .0164). The median OS in the investigative arm was 10.8 months (95% CI, 9.2-12.9) versus 9.7 months (95% CI, 8.6-10.7) in the control arm. At 12 months, the OS rates in the pembrolizumab/EP and placebo/EP arms were 45.1% versus 39.6%, respectively, whereas at 24 months, these rates were 22.5% and 11.2%, respectively.

TO READ MORE, VISIT bit.ly/389Qx36.
Zotiraciclib Combo Demonstrates Early Efficacy in Recurrent High-Grade Gliomas

Zotiraciclib, a potent CDK9 inhibitor, was found to induce clinically meaningful efficacy with a tolerable safety profile in patients with recurrent, high-grade gliomas when used in combination with temozolomide.

The finding was based on top-line data from a phase 1b-17-C-0009 trial (NCT02942264). The trial met or exceeded the predetermined end point of progression-free survival and successfully identified the recommended dose of the doublet. Based on these data, the clinical-stage biopharmaceutical company Adastra Pharmaceuticals is working on launching a registration-enabling trial that will examine the doublet in patients with recurrent high-grade gliomas. The company also seeks to broaden the application of zotiraciclib/temozolomide to other solid tumors and hematologic malignancies.

The trial was performed in 2 stages: a maximum-tolerated dose (MTD)-finding stage and a cohort extension. In the MTD-finding portion of the research, temozolomide was evaluated in 2 alternate schedules, dose-dense and metronomic, in combination with zotiraciclib. The cohort extension portion of the trial evaluated the MTD for each schedule and the treatment arm that showcased the better response would be chosen for the combination in a phase 2 trial.

The combination was found to be tolerable in this patient population. All participants who experienced dose-limiting toxicities recovered. Moreover, 10% of patients (n = 4) finished 12 cycles of treatment and they achieved prolonged disease control. Notably, 10% of patients experienced a reduction in tumor size.

TO READ MORE, VISIT bit.ly/3u0wRb3.

Biond Biologics and Sanofi Set Plans for License Agreement for BND-22

Biond Biologics Ltd and Sanofi will join an exclusive worldwide license agreement for the development and commercialization of the novel immuno-therapy BND-22.

The agreement stipulates that Biond will receive a $125 million up-front payment in cash and will be entitled to receive more than $1 billion in development, regulatory, and sales milestones, as well as tiered double-digit royalty payments.

BND-22, a humanized IgG4 antibody antagonist that targets the Ig-like transcript 2 receptor, demonstrated broad antitumor activity by targeting ILT2-mediated “do-not-eat-me” signals in macrophages and by activating natural killer and CD8-positive lymphocytes in preclinical studies.

BND-22 will be evaluated for safety and tolerability alone and in combination with approved cancer therapies in patients with advanced malignancies in its first-in-human phase 1a study (NCT04717375). Following evaluation of potential correlations between antitumor activity of BND-22 and select tumor and blood-based biomarkers, Sanofi will assume all clinical development and commercialization responsibilities.

TO READ MORE, VISIT bit.ly/3dclYMp.

Dana-Farber Launches First Venture Fund

Dana-Farber Cancer Institute has announced the launch of Binney Street Capital, LLC, its first venture fund designed to advance its mission of developing options for incurable cancers.

The primary focus of the fund will be therapeutics, while also considering investments in novel diagnostics, digital health, and services companies. Investments will be directed toward startup companies that are either created with Dana-Farber intellectual property or are cofounded by a Dana-Farber investigator.

“It’s a fairly new, exciting effort,” said Luba Greenwood, managing partner of Binney Street Capital, in an interview with OncologyLive®. “There are other types of investors in oncology, but they are not cancer institutes….We can continue to find some really amazing therapies, help them grow, help our scientists start companies in really exciting areas, and then take the money and reinvest it back into the science and help the scientists again.”

Binney Street Capital will be helmed by an advisory group of leading investors and industry experts dedicated to advancing Dana-Farber’s mission. Plans for the first 3 years include investments in 8 to 10 companies ranging from $250,000 to $2 million.

TO READ MORE, VISIT bit.ly/3dkKigb.

Novartis Inks Licensing Agreement With BeiGene for Tislelizumab

Novartis has signed a strategic collaboration agreement with BeiGene, Ltd, to in-license the anti–PD-1 monoclonal antibody tislelizumab (BGB-A317) in various markets outside of China.

Novartis will pay BeiGene an up-front cash payment of $650 million plus royalties, per the agreement. The agreement allows Novartis to develop and market the PD-1 inhibitor in the United States, Canada, Mexico, the European Union, the United Kingdom, Norway, Switzerland, Iceland, Liechtenstein, Russia, and Japan. Additionally, the agreement allows for payment up to $1.3 billion based on regulatory indications and up to $250 million based on sales targets. BeiGene will retain the rights to tislelizumab in China and other countries.

The agent, which is not approved in the United States, gained clearance in December 2019 from the China National Medical Products Administration (NMPA) for the treatment of patients with classical Hodgkin lymphoma. Additionally, the NMPA approved tislelizumab as treatment for patients with PD-L1–high, previously treated advanced or metastatic urothelial carcinoma; and patients with non–small cell lung cancer.

TO READ MORE, VISIT bit.ly/2OKqWHj.
In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:

**29%**

reduction in risk of PFS event*  
(HR: 0.71; 95% CI: 0.54, 0.93; P = 0.011); median PFS 48.2 vs 20.8 months for A+CHP and CHOP, respectively; primary endpoint**

*PFS was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease.

**Indication**

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

**Important Safety Information**

**BOXED WARNING**

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

**Contraindication**

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

**Warnings and Precautions**

- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
**ECHELON-2 trial design:** A multicenter, phase 3, randomized, double-blind, double-dummy, actively controlled trial in 452 patients with sALCL and other CD30-expressing PTCL. Patients were randomized 1:1 to A+CHP (n = 226) or CHOP (n = 226), and received treatment every 3 weeks for 6 to 8 cycles at investigator’s discretion. Primary endpoint was PFS per IRF, defined as progression, death from any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease. Overall survival was a key secondary endpoint.¹ ³

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

Anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.²

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

**reduction in risk of death**

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

†Median overall survival follow-up of 42.1 months with A+CHP and CHOP; median overall survival not reached in either treatment arm.²
Important Safety Information, cont’d

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

- **Hematologic toxicities**: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS.
  
  Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma or previously untreated PTCL.
  
  Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

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

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

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

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

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

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

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

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

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

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

**Most Common (≥20% in any study)**

**Adverse Reactions**

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

**Drug Interactions**

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

**Use in Specific Populations**

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

**Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages and full Prescribing Information at** [adcetrispro.com](http://adcetrispro.com)

**References**


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ADCyris® (brentuximab vedotin) for injection, for intravenous use
Initial U.S. approval: 2011
Brief Summary: see package insert for full prescribing information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
JC virus infection resulting in PML and death can occur in patients receiving ADCyris.

1 INDICATIONS AND USAGE
ADCyris is a CD19-directed antibody-drug conjugate indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD19-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL, not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
For dosing instructions of combination agents administered with ADCyris, see the manufacturer's prescribing information.
Administer ADCyris as a 30-minute intravenous infusion. The recommended dose is 1.8 mg/kg up to a maximum of 180 mg in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) administered every 3 weeks with each cycle of chemotherapy for 6 to 8 doses. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance [CrCl] <50 mL/min). The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

2.2 Recommended Prophylactic Medications
In patients with previously untreated PTCL, who are treated with ADCyris + CHP, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification
Peripheral Neutropenia: For Grade 2 motor neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 sensory neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 motor neuropathy, discontinue dosing. For Grade 4 sensory or motor neuropathy, discontinue dosing. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.
Neutropenia: For Grade 3 or 4 neutropenia, administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

4 CONTRAINDICATIONS
ADCyris is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

5 WARNINGS AND PRECAUTIONS
5.1 Peripheral Neuropathy
ADCyris treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCyris-induced peripheral neuropathy is cumulative.
In ECHLON-2 (Study 6), 52% of patients treated with ADCyris + CHP experienced new or worsening peripheral neuropathy of any grade by maximum grade, 44% Grade 1, 16% Grade 2, 11% Grade 3, <1% Grade 4. For Grade 3 motor neuropathy, discontinue dosing. For Grade 4 sensory or motor neuropathy, discontinue dosing. Of patients with residual neuropathy at their last evaluation, the neuropathy was Grade 1 in 72%, Grade 2 in 25%, and Grade 3 in 3%.
Monitor patients for symptoms of neuropathy, such as hyporeflexia, hyperreflexia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCyris.

5.2 Anaphylaxis and Infusion Reactions
Infusion-related reactions, including anaphylaxis, have occurred with ADCyris. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCyris and administer appropriate medical therapy.
If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities
Fatal and serious cases of febrile neutropenia have been reported with ADCyris. Prophylaxis (100 mg/kg) should be initiated at least 24 hours before the first dose of ADCyris, with or without G-CSF. In the event of febrile neutropenia, discontinuation of ADCyris may be required.

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

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

5.6 Increased Toxicity in the Presence of Severe Renal Impairment
The frequency of Grade 3/4 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MAAE exposure, Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCyris in patients with severe renal impairment (CrCl <30 mL/min).

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment
The frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with no hepatic dysfunction. Avoid the use of ADCyris in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

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

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

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

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

5.12 Gastrointestinal Complications
Fatal and serious events of acute pancreatitis have been reported. (Fatal and serious gastrointestinal [GI] complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, necrotic colitis, and diarrhea, lymphoma with pre-existing GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, ADCyris can cause fetal harm when administered to a pregnant woman. There are no adequately and well-controlled studies of ADCyris in pregnant women. In animal reproduction studies, brentuximab vedotin caused embryofetal toxicities, including significantly decreased fetal viability and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every 3 weeks.
Advise females of reproductive potential to avoid pregnancy during ADCyris treatment and for at least 6 months after the final dose of ADCyris. Advise a pregnant woman of the potential risk to the fetus.

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

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

ADCCRTIS in combination with CHP was evaluated in patients with previously untreated, CD30-expressing PTCL, in a multicenter, randomized, double-blind, double-dummy, active-controlled trial. Patients were randomized to receive ADCCRTIS + CHP or CHOP for 6 to 8, 21-day cycles. ADCCRTIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/m² intravenously over 30 minutes, approximately 1 hour after completion of CHP. The trial required hepatic transaminases ≤3 times the upper limit of normal (ULN); total bilirubin ≤1.5 times ULN; and serum creatinine ≤2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy.

A total of 449 patients were treated (233 with ADCCRTIS + CHP; 226 with CHOP), with 6 cycles planned in 81%. In the ADCCRTIS + CHP arm, 72% of patients received 8 cycles, and 18% received 6 cycles. Primary prophylaxis with G-CSF was administered to 94% of ADCCRTIS + CHP-treated patients and 77% of CHOP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the CHOP arm and 4% of patients in the ADCCRTIS + CHP arm; most often from infection. Serious adverse reactions were reported in 38% of ADCCRTIS + CHP-treated patients and 35% of CHOP-treated patients. Serious adverse reactions occurring in ≥2% of ADCCRTIS + CHP-treated patients included febrile neutropenia (14%), pneumonia (9%), pyrexia (1%), and sepsis (8%).

The most common adverse reactions observed ≥2% more in recipients of ADCCRTIS + CHP were nausea, diarrhoea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥10%) adverse reactions observed ≥2% more with ADCCRTIS + CHP were febrile neutropenia, abdominal pain, decreased appetite, dyspnoea, edema, cough, dizziness, hypokalaemia, increased weight, and myalgia. In recipients of ADCCRTIS + CHP, adverse reactions led to dose delays of ADCCRTIS in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCCRTIS with or without the other components in 7% (most often from peripheral neuropathy and infection).

Table 7: Adverse Reactions Reported in >10% of ADCCRTIS + CHP-Treated Patients with Previously Untreated, CD30-Expressing PTCL (Study 6, ECHELON-2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCCRTIS + CHP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>66 13 &lt;1</td>
<td>59 12 &lt;1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>59 17 22</td>
<td>58 14 22</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>51 18 1</td>
<td>57 18 2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>19 17 2</td>
<td>16 12 4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17 3 3</td>
<td>13 3 2</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46 2</td>
<td>38 2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>38 6</td>
<td>20 &lt;1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>32 2</td>
<td>27 3</td>
</tr>
<tr>
<td>Constipation</td>
<td>28 &lt;1</td>
<td>10 1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 &lt;1</td>
<td>17 2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17 1</td>
<td>13 &lt;1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>52 1 &lt;1</td>
<td>55 4</td>
</tr>
<tr>
<td>Headache</td>
<td>15 &lt;1</td>
<td>15 &lt;1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 -</td>
<td>9 &lt;1</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>35 2</td>
<td>29 2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28 1 &lt;1</td>
<td>18 &lt;1</td>
</tr>
<tr>
<td>Edema</td>
<td>15 &lt;1</td>
<td>12 &lt;1</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 &lt;1</td>
<td>15 &lt;1</td>
</tr>
</tbody>
</table>

Table 7: Adverse Reactions, cont’d

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCCRTIS + CHP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin and subcutaneous disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>20 -</td>
<td>7 &lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>18 1 &lt;1</td>
<td>14 1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>11 -</td>
<td>8 -</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>15 2</td>
<td>11 2</td>
</tr>
<tr>
<td>Cough</td>
<td>13 &lt;1</td>
<td>10 -</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17 1</td>
<td>12 1</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>12 4</td>
<td>8 &lt;1</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>12 &lt;1</td>
<td>8 &lt;1</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 -</td>
<td>14 -</td>
</tr>
</tbody>
</table>

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

The table includes a combination of grouped and ungapped terms. CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone. Events were graded using the NCI-CTCAE Version 4.03.

Additional Important Adverse Reactions

In a study of ADCCRTIS in combination with CHP [Study 6, ECHELON-2], infusion-related reactions were reported in 10 patients (4%) in the ADCCRTIS + CHP-treated arm; 21% of patients with events that were Grade 3 or higher events, and 8% (4%) patients with events that were less than Grade 3.

Pulmonary Toxicity

In a trial in patients with CHL, that studied ADCCRTIS with bortezomib as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (bortezomib, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnoea, interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The coadministration of ADCCRTIS with bortezomib is contraindicated.

In a study of ADCCRTIS in combination with CHP [Study 6, ECHELON-2], non-infectious pulmonary toxicity events were reported in 5 patients (2%) in the ADCCRTIS + CHP arm; all 5 patients were pneumonitis.

6.2 Post Marketing Experience

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

Blood and lymphatic system disorders: febrile neutropenia.

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

Hepatobiliary disorders: hepatotoxicity.

Infections: Pneumonia, serious infections and opportunistic infections.

Metabolism and nutrition disorders: hyperglycemia.

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

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

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADCCRTIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 10% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-breutuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-breutuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (92%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-breutuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE, which may increase the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations. See Data. The available data from case reports on ADCETRIS use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise a pregnant woman of the potential risk to a fetus.

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

Data
Animal Data
In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 8 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (>99%), post-implantation loss (>99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and multiply affected hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

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

8.3 Females and Males of Reproductive Potential

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

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

Contraception

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

Males

ADCETRIS may damage spermatogenesis and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 8 months after the final dose of ADCETRIS.

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study B E68072-2), 31% of ADCETRIS + CHP-treated patients were age 65 or older. Among older patients, 24% had toxicities of Grade 3 and 4, 6% had serious adverse reactions. Among patients younger than age 65, 21% had adverse reactions of Grade 3 and 33% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 29% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (GFR <30 mL/min).

No dosage adjustment is required for mild (GFR >30–60 mL/min) or moderate (GFR 10–30 mL/min) renal impairment.

8.7 Hepatic Impairment

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

10 OVERDOSE

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

17 PATIENT COUNSELING INFORMATION

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

Fever/Neutropenia: Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

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

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

Progressive Multifocal Leuкоencephalopathy: Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms:

• changes in mood or usual behavior
• confusion, thinking problems, loss of memory
• changes in vision, speech, or walking
• decreased strength or weakness on one side of the body

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

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

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

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm.

Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 8 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcertris.com

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Margetuximab approval augments emerging treatment choices

by ANITA T. SHAFFER

Margetuximab-CMKB (Margenza) represents an effective new therapeutic option that can be combined safely with a chemotherapy drug of choice for patients with metastatic HER2-positive breast cancer who have undergone multiple lines of prior treatment, according to Hope S. Rugo, MD, FASCO.

In December 2020, the FDA approved margetuximab in combination with chemotherapy for adults with metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2 regimens, at least 1 of which in the metastatic setting.

The approval for margetuximab was based on findings from the phase 3 SOPHIA trial (NCT02492711), in which 536 patients were randomized to receive either margetuximab or trastuzumab (Herceptin) plus physician’s choice of capecitabine, eribulin, gemcitabine, or vinorelbine.

After 24 months of treatment and follow-up, the median progression-free survival (PFS) by blinded independent central review was 5.8 months (95% CI, 5.5-7.0) for patients in the margetuximab arm and 4.9 months (95% CI, 4.2-5.6) for patients in the trastuzumab group (HR, 0.76; 95% CI, 0.59-0.98; P = .033).

In a second planned interim analysis conducted after 430 PFS events, investigator-assessed median PFS showed a 29% risk reduction with margetuximab therapy (HR, 0.707; 95% CI, 0.580-0.862; stratified log-rank P = .0006). In an analysis conducted after 270 deaths, median overall survival (OS) was 21.6 months (95% CI, 18.86-24.05) with margetuximab vs 19.8 months (17.54-22.28) with trastuzumab (HR, 0.89; 95% CI, 0.69-1.13; P = .33). Investigators expect the final OS analysis to be available in 2021, after 385 events occur.

Rugo, a lead investigator on the SOPHIA trial, discussed the implications of the margetuximab approval in an interview. A 2020 Giants of Cancer Care® award winner in Education, Rugo is a professor in the Department of Medicine and the director of breast oncology and clinical trials at the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center.

What does margetuximab bring to the table for patients with HER2-positive breast cancer?

Margetuximab is a novel HER2-targeted antibody. Fc engineering was performed on the antibody that altered Fc receptor affinities. The Fab fragment has the same specificity and affinity and disrupts HER2 signaling similar to trastuzumab. But the Fc component of the antibody has been engineered to increase affinity for the activating Fcγ receptor (FcγR) IIIA, which is called CD16A, and to decrease the affinity for the inhibitory FcγRIIB, which is CD32B.

How does the structure of margetuximab contribute to its efficacy?

The intent of enhancing the affinity for certain IgG FcγRs and decreasing the affinity for the inhibitory receptors is to enhance innate immunity and antibody-dependent cellular cytotoxicity (ADCC) to increase CD16A engagement, which then would result in more potent ADCC stimulation. For the inhibitory factor, if you have less effect on the inhibitory receptor, you could enhance adaptive immunity with HER2-specific T-cell reactivity and antibodies.

Reduced CD32 binding theoretically would result in enhanced immune activation, which we know is very important for the activity of trastuzumab and now it appears other antibodies as well. In a phase 1 study (NCT01148849), some patients were able to stay on margetuximab for many years, even though they had trastuzumab-resistant disease when they started on study. Clearly, there is a unique effect of margetuximab in HER2 targeting.

What is the potential impact of genotype on therapy response?

We looked at overall survival and PFS subgroups, but we also knew that CD16A biology could impact trastuzumab outcome. In adjuvant trials, it appeared that patients didn’t do quite as well with the addition of trastuzumab if they carried this low-affinity CD16A receptor, CD16A [genotypes containing a] 158F [allele]. This different binding affinity is very, very interesting.

This idea of looking at the patients who are F [allele] carriers is fascinating, and it’s being studied in an ongoing neoadjuvant trial. This was a prespecified, exploratory subset; we are not using this in decisions about which patients should receive margetuximab in the metastatic setting in combination with chemotherapy. The MARGOT trial (NCT04425018) in our [Translational Breast Cancer Research Consortium] is specifically enrolling patients who have an F allele. [Participants] are randomized to receive margetuximab or trastuzumab as their neoadjuvant primary HER2-targeted antibody. This is a good trial and will tell us a lot. You have untreated patients, and you’ll be able to see whether or not there is any difference in terms of the efficacy of margetuximab in a prospective trial based on their CD16 genotype. Patients also receive pertuzumab [Perjeta].

Where does margetuximab fit into the treatment landscape for metastatic breast cancer?

We’re thinking about using this in the later-line setting as we move pertuzumab as well as T-DM1 [ado-trastuzumab emtansine (Kadcyla)] to the earlier-stage setting and higher-risk disease, and we’re looking at moving fam-trastuzumab...
**BASELINE PATIENT CHARACTERISTICS:**

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>Margetuximab plus chemotherapy (n = 266)</th>
<th>Trastuzumab plus chemotherapy (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3+</td>
<td>44.0%</td>
<td>47.4%</td>
</tr>
<tr>
<td>ISH amplified</td>
<td>56.0%</td>
<td>52.6%</td>
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<tr>
<td><strong>Hormone receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive*</td>
<td>61.7%</td>
<td>63.0%</td>
</tr>
<tr>
<td>Negativeb</td>
<td>38.3%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Estrogen receptor–positive and/or progesterone receptor–positive status.
*bEstrogen receptor–negative and progesterone receptor–negative status.

**Prior lines of anti-HER2 therapy**

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab plus chemotherapy</th>
<th>Trastuzumab plus chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8.6%</td>
<td>10.4%</td>
</tr>
<tr>
<td>3</td>
<td>46.6%</td>
<td>40.4%</td>
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<tr>
<td>2</td>
<td>42.1%</td>
<td>48.1%</td>
</tr>
<tr>
<td>1</td>
<td>2.6%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

**Efficacy Results in the Phase 3 Sophia Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Margetuximab plus chemotherapy (n = 266)</th>
<th>Trastuzumab plus chemotherapy (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.8 (5.5-7.0)</td>
<td>4.9 (4.2-5.6)</td>
</tr>
<tr>
<td>Efficacy for patients with measurable disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>22% (17%-27%)</td>
<td>16% (12%-20%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>6.1 (4.1-9.1)</td>
<td>6.0 (4.0-6.9)</td>
</tr>
</tbody>
</table>

**Commonly Reported Adverse Events in Phase 3 Sophia Trial**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Margetuximab plus chemotherapy (n = 264)</th>
<th>Trastuzumab plus chemotherapy (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3 or 4</td>
<td>All grades</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>57%</td>
<td>47%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Constipation</td>
<td>19%</td>
<td>17%</td>
</tr>
</tbody>
</table>
deruxtecan-nxki [Enhertu] and the tucatinib [Tukysa] triplet earlier. Margetuximab will be a next-line agent in combination with a menu of chemotherapy agents.

Today, margetuximab is moving forward as an option for treatment of patients with metastatic HER2-positive breast cancer. I think this question about whether or not we could select patients specifically based on their genotype to receive one antibody versus another is fascinating. We've really not made big headway in pharmacogenomics overall in breast cancer, so I think this is an exciting step.

Q How does the adverse effect profile of margetuximab compare with that of trastuzumab?

Overall, the number of adverse events with margetuximab versus trastuzumab [was] equivalent. Adverse events that were either chemotherapy- or antibody-related were similar, with the exception of infusion-related reactions. There were clearly more infusion-related reactions in patients who were treated with margetuximab vs trastuzumab. Now it’s important to remember that everybody who was in this trial had already received prior trastuzumab and pertuzumab, except for 1 patient, and over 90% had also received T-DM1, so they had already sort of had the test of time in terms of infusion reactions, which can also occur with the first infusion.

If you look at grade 3 or [higher] infusion reactions, there were 4 with margetuximab and 0 for trastuzumab out of about 265 patients in [each] arm, so [they’re] not very common. Overall, including grade 1 and grade 2, [infusion-related reactions were] 13.3% versus 3.4% for trastuzumab and margetuximab, [respectively]. Most of them were easily controlled with premedications and certainly were controlled with rescue [therapy] at the time of developing these [adverse] effects. For the grade 3 or greater [infusion-related reactions], 2 of the patients discontinued therapy but, again, this was earlier in the trial and people weren’t really aware [of] how to manage this. With additional premedications, the other 2 patients continued on treatment.

Clearly, this is something we need to know about, but we can manage it. We see infusion-related reactions with a number of different antibody-based drugs that are approved. We always need to be aware of that when we’re infusing antibodies like this and be able to react and treat so that we can continue therapy.

Q Is there anything else important to note about administering this drug?

It’s probably worthwhile to start with some degree of premedication when you give margetuximab. Keep in mind as you start speeding up the infusion that you want to be sure that patients tolerate it with the first infusion, but also don’t be afraid if they do develop a reaction. You can stop, give additional medications, and usually complete the infusion or delay and give the infusion on a different day. That hasn’t been a big problem for us overall—it’s just important to know about. In terms of clinical practice, where we are using margetuximab— or thinking about it in terms of our sequencing of therapy—is after trastuzumab deruxtecan and after the tucatinib triplet....But it’s important to keep in mind that both of these agents have their own toxicities. [Some patients] might be eligible to receive margetuximab sooner.

REFERENCES

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PROGRAM OVERVIEW

• Nominations are open through April 16, 2021.
• Domestic and international nominations will be accepted.
• The Giants of Cancer Care® steering committee will vet all nominations to determine finalists in each category.
• A selection committee of more than 120 oncologists will vote to determine the 2021 inductees.
• The 2021 Giants of Cancer Care® class will be announced in the fall of 2021.
IN A RESEARCH CAREER that has spanned 3 decades, John L. Marshall, MD, has participated in all phases of clinical trials. He was at the forefront of research into immunotherapy and targeted therapy for gastrointestinal (GI) cancers and helped to establish standards of care for patients with metastatic colorectal cancer (CRC). He explored vaccines for CRC in the late 1990s.

But his focus sharpened in 2006 after his wife, Liza Marshall, received a diagnosis of stage IIIA near-inflammatory triple-negative breast cancer. She is in better health today, but he was frustrated by the unanswered questions in cancer care. “We should be in more of a hurry to cure cancer,” Marshall said in Off Our Chests — A Candid Tour Through the World of Cancer, a book he coauthored with his wife about her cancer journey. “I could not understand why there was no sense of panic among the research and advocacy communities.”

Since then Marshall has concentrated on early-phase trials, particularly genomic and biomarker studies, looking for giant leaps in GI cancer care rather than small steps. He has yet to find the major advance he’s looking for but believes that investigators are getting closer. In February, the American Society of Clinical Oncology (ASCO) named molecular profiling in GI cancers as the 2021 Advance of the Year in oncology.1

“The HER2-positive story gets better and better. The IO [immuno-oncology] story gets better and better across different diseases,” he said in an interview with OncologyLive®. “There was clear evidence of progress in each of the fronts but we’re still waiting on that big sea change. We don’t have it quite yet.”

Marshall has made it his mission to improve the lives of patients with GI cancers through innovative research, personalized medicine, and focused advocacy at Georgetown University’s Otto J Ruesch Center for the Cure of Gastrointestinal Cancer, which he helped establish in 2008. He serves as director of the center, holds the Frederick P. Smith Chair of Medicine, and is chief of the Division of Hematology/Oncology with Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, DC.

He said some of the most interesting trials being conducted at the moment involves treating patients in basket studies exploring agents targeting narrower and narrower genetic mutations. Investigators are zeroing in specifically on the KRAS G12C mutation, which is associated with a poor prognosis and lack of response to standard treatments. The mutation is found in approximately 14% of lung adenocarcinomas, 3% to 4% of CRCs, and 1% to 2% of other solid tumors.2

Although there are no approved therapies targeting the KRAS G12C alteration, several agents are advancing in clinical development, notably in non–small cell lung cancer and CRC. Adagrasib (MRTX849) monotherapy resulted in a 17% objective response rate (ORR) among 18 evaluable patients with advanced CRC harboring the mutation, according to findings from the phase 1/2 KRYSTAL-1 trial (NCT03785249).2 Sotorasib (formerly AMG 510) demonstrated a 7.1% ORR across dosing levels among 42 patients with heavily pretreated metastatic KRAS G12C-mutated CRC, according to findings from the phase 1/2 CodeBreak 100 trial (NCT03600883).3

“Right molecular biomarker, right drug, best outcome,” Marshall said. “That’s the coolest thing that’s happening in oncology.”
GETTING THE LATEST ON GI CANCER

Marshall helps shape the conversation about important developments across the GI cancer field during an annual conference hosted by Physicians’ Education Resource®, LLC (PER®). This year, he served as cochair of the 6th Annual School of Gastrointestinal Oncology® (SOGO®) on March 20, along with Michael A. Choti, MD, MBA, division chief of surgery at Banner MD Anderson Cancer Center in Gilbert, Arizona, and an internationally recognized pancreatic-hepatobiliary surgeon and surgical oncologist.

The virtual multitrack symposium features general session presentations on important concepts and debates, educational tracks exploring locoregional treatment of GI cancers and management of advanced GI cancers, SOGO® seminars, and select case-based discussions on multidisciplinary, real-world management of GI cancers.

Marshall said the program always includes hot topics in cancer care. This year, organizers felt that the most important subject in oncology is racial inequalities in outcomes and access to care. Marcus S. Noel, MD, associate professor of medicine and codirector of the Clinical Research Management Office at Georgetown University Medical Center, is scheduled to deliver a keynote address exploring racial disparities in GI cancer.

“The second major volatile topic that’s out there is the cost of health care,” Marshall said. “We know that right now, there are ongoing discussions about balancing the rising cost of drugs and the need for innovation.”

The coronavirus disease 2019 pandemic has taught the medical world that it is vital to mobilize science in the pharmaceutical industry, Marshall noted. A high-end pharmaceutical network is critical to our existence and our health, but it’s also expensive. Medical innovations have improved care while also raising cost, which makes those innovations less accessible.

“That’s true around the world, too, if you think about the global impact of cancer,” Marshall said. “We in the United States, for all of our fussing about calling insurance [for coverage], we have unlimited access compared to the rest of the world. So how do we get some of these novel approaches to those patients out there, particularly these breakthrough therapies for these smaller and smaller subgroups of molecularly defined patients? How do we get those patients the drugs that they need, wherever they are on the planet?”

Marshall said the SOGO® program would address the most critical clinical issues of the day including molecular profiling, multidisciplinary care, neoadjuvant therapies, reducing toxicity, and combined modality approaches.

“We’re trying to put each other out of business,” Marshall said. “We’re trying to put the surgeons out of business with chemoradiation. We’re trying to put the radiation oncologist out of business with better chemotherapy and better surgery. We’re trying to make the same outcomes or better and affect patients less, with fewer adverse effects, shorter treatments, and less toxicity.”

MOLECULAR PROFILING IS THE KEY

During the course of his career, Marshall has served as principal investigator for more than 100 clinical trials in CRC and other GI malignancies. His work on novel therapies includes studies of
erlotinib (Tarceva), the EGFR inhibitor; obatoclax (GX15-070), a Bcl2 mimetic that binds to a broad spectrum of BCL2 regulator proteins; and dendritic cell vaccines for CRC. He also has been a leading investigator into chemotherapy regimens.

In 2003, Marshall was part of a team that established FOLFOX4 (leucovorin, 5-fluorouracil [5-FU], and oxaliplatin) as the standard of care for second-line treatment of metastatic CRC. The combination improved response rate, time to tumor progression, and tumor-related symptoms compared with 5-FU/leucovorin. At the time, there was no effective second-line therapy for patients with progressive metastatic CRC.4

Three years later, he coauthored findings demonstrating a survival benefit for FOLFIRI (leucovorin, 5-FU, and irinotecan) and FOLFIRI plus bevacizumab (Avastin) in patients with treatment-naïve metastatic CRC. In findings published in the Journal of Clinical Oncology, the median progression-free survival (PFS) was 7.6 months for patients assigned FOLFIRI compared with 5.9 months for those assigned to irinotecan plus bolus FU/leucovorin (mIFL) and 5.8 months for those assigned to irinotecan plus oral capcitabine (CapEIRI). After adjusting the protocol to add bevacizumab, the median overall survival (OS) was not reached for the FOLFIRI/bevacizumab combination compared with 19.2 months for mIFL/bevacizumab (P = .007).5

In 2015, he established and directed the Precision Oncology Alliance, a collaborative network of more than 40 cancer centers working with Caris Life Sciences, a Texas-based company, to study the impact of molecular profiling on cancer research, value, and outcomes.6

Marshall said he has watched enviously as his colleagues who treat patients with cancers compared with that of breast cancer. Naturally, a part of him felt as if his public preaching was karma once he received news of his wife’s diagnosis.

“You can’t be it forever. The emotional load that that takes is what leads me to want to be that empathetic, all-the-time caregiver and going crazy, right? We have to watch ourselves to not be cold and callous—because then we’re not doing the job right either—but not being so far over [on the other wall] and not doing the job right either—but not being so far over [on the other wall] that they may or may not speak about their treatment-related adverse events.

“Going through such a personal experience with his wife has changed the way John approaches his patients with GI cancers, although it took some fine-tuning.

“I used to have this vision in my head that there was this half-built wall; I was on this side, and the patient is on that side. I could shake their hand and I could examine them—but they were over there, and I was over here. After Liza’s diagnosis and our experience going through all of this, I couldn’t find that wall anymore. I was over there [on the same side as the patients], giving out [my email address] and trying to be responsive,” John said. “There is that line of wanting to be that empathetic, all-the-time caregiver and going crazy, right? You can’t be it forever. The emotional load that that takes is what leads me to burnout and leads others to burnout.

“We have to watch ourselves not be cold and callous—because then we’re not doing the job right either—but not being so far over [on the other wall] that we burn out emotionally. Everybody is going to have to draw that line and develop that strategy. We’re not superhuman; we are human. What we do every day is the most human thing that you can do, and that’s care for others.”
lung cancer leverage an expanding menu of molecularly targeted therapies. Recently, however, the GI field has made progress toward several new targets, including BRAF and HER2. The 2 advances specifically cited in the ASCO report were FDA approvals for fam-trastuzumab deruxtecan-nxki (Enhertu) for previously treated locally advanced or metastatic HER2-positive gastric or gastroesophageal adenocarcinoma, and for pembrolizumab (Keytruda) for the first-line treatment of patients with unresectable or metastatic CRC that is microsatellite instability-high or mismatch repair–deficient.1

Such developments highlight the impact of tumor profiling. “It is so important for us as oncologists to make sure we’re doing the best molecular testing,” Marshall said. “You need to do it right from the beginning... so that you know all of the chess pieces on the chessboard because they’re not common. And unless you look under every single rock, you’ll never find it.

“With so many new approvals in this space, [there are] so many options for all of these patients that deliver not just minor benefits, but major benefits,” he added. “You can’t miss these opportunities. They won’t come every day. But when you find them, it’s pretty cool.”

Meanwhile, Marshall said much work remains in delineating early intervention strategies throughout the GI cancer field. “In the adjuvant and neoadjuvant world, I think we are all struggling with how to incorporate things like microsatellite instability into neoadjuvant approaches,” he said. “On the one hand, we have data that says chemotherapy is harmful in the space. On the other hand, we don’t know any better—we don’t have IO approval in that space for neoadjuvant approaches. Those studies are going to be critical to how we approach those patients from the beginning, not just in the metastatic setting.”

Not all patients with GI cancers are deriving benefit from frontline therapy with immune checkpoint inhibitors. For some, chemotherapy induces better results, at least for a short time. Marshall said he is looking forward to results from trials studying combinations of checkpoint inhibitors with chemotherapy or other immunotherapy or agents in earlier lines of therapy.

“We have to remember, first, that it was only 10 years ago when no one on the planet except for a few people thought immunotherapy was ever going to have an impact at all,” he said. “We thought that was crazy. Why bother? And it was really these checkpoint inhibitors that were a breakthrough. Now we’re saying, ’How come they’re not working everywhere?’ We should get them to work in every cancer, and that’s not happening so far.”

One of the few GI cancers where immunotherapy has shown signs of making a difference is hepatocellular carcinoma (HCC), traditionally one of the most difficult cancers to treat. Since 2017, the PD-1 inhibitors pembrolizumab and nivolumab (Opdivo) have gained approvals as monotherapy in second-line HCC settings; nivolumab also is indicated in combination with ipilimumab (Yervoy) for previously treated patients with HCC.

The FDA is now taking another look at 2 of those approvals, which were granted under the agency’s accelerated pathway. The monotherapy approvals for pembrolizumab and nivolumab in HCC are among the immunotherapy indications that will be reevaluated as part of an industry-wide review of accelerated approvals in oncology “in which confirmatory trials did not confirm clinical benefit,” according to the FDA.8

Those indications are among 6 that will be discussed during an Oncologic Drugs Advisory Committee public hearing scheduled from April 27 to 29. An indication for pembrolizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma that expresses PD-L1 and has progressed after 2 or more prior lines of therapy also will be reviewed.8 Other indications for these agents are not affected, including those in HCC and gastric cancers.

Meanwhile, immunotherapy has been gaining ground in earlier therapeutic settings in HCC. In May 2020, the FDA approved atezolizumab (Tecentriq), a PD-L1 inhibitor, in combination with bevacizumab for
patients with unresectable or metastatic HCC who have not received prior systemic therapy. The approval was based on findings from the phase 3 IMbrave150 trial (NCT03434379), in which the atezolizumab regimen showed an OS benefit compared with sorafenib (Nexavar). The median OS was not reached for participants who received atezolizumab followed by bevacizumab vs 13.2 months (95% CI, 10.4-not estimable) in those treated with sorafenib monotherapy (HR, 0.58; 95% CI, 0.42-0.79; P = .0006). The estimated median PFS was 6.8 months (95% CI, 5.8-8.3) vs 4.3 months (95% CI, 4.0-5.6), respectively (HR, 0.59; 95% CI, 0.47-0.76; P < .0001). The next challenge, Marshall said, is learning how to turn cold tumors—those that don’t respond to immunotherapy—into hot tumors. It is not clear yet whether the immune system cannot see cold tumors or whether the tumor’s defenses against the immune system are too strong to allow a response.

“What we are seeing in liver cancers and bile duct cancers and some others [is that] combinations of therapies are resulting in improved outcomes from immunotherapies,” he said. “The Holy Grail right now is in microsatellite-stable colon cancers and pancreas cancers. These are tough nuts to crack with regard to immunotherapy.”

**MACHINE LEARNING IS THE FUTURE OF CANCER CARE**

Marshall said artificial intelligence (AI) is, surprisingly, one of the biggest developments driving improvements in cancer care. Automated algorithms can extract meaningful patterns that provide practical knowledge and change the way in which treatments are developed, patients are classified, and diseases are studied.

Using computers to analyze genomic data from patients with cancer, investigators can identify up to 100,000 mutations for each tumor sample, although the clinical significance is unclear. AI applications in imaging, genomics, and personalized medicine are expected to expand in multiple oncology settings. With more and more assays collecting information, AI will be vital to interpreting and applying the data.

Marshall was part of a team that in February 2021 published findings from a study evaluating a machine-learning approach called FOLFOXai applied to clinical and next-generation sequencing data from a real-world evidence (RWE) dataset. Investigators collected RWE outcomes data from the Caris Life Sciences Precision Oncology Alliance registry and insurance claims data from more than 10,000 physicians. They then conducted a blinded retrospective-prospective analysis of samples from patients enrolled in the phase 3 TRIBE2 study (NCT02339116). Next-generation sequencing analysis was performed for further clinical validation.

In TRIBE2, patients with unresected metastatic colorectal cancer (N = 679) were assigned to FOLFOX/bevacizumab followed by FOLFIRI/bevacizumab after progression or FOLFOXIRI/bevacizumab followed by the reintroduction of the same regimen after progression. Blinded analysis showed that FOLFOXai was predictive for OS in both oxaliplatin-containing treatment arms of TRIBE2 (FOLFOX; HR, 0.629; P = .04; FOLFIRI, HR, 0.483; P = .02).

FOLFOXai also predicted treatment benefit from oxaliplatin-containing regimens in patients advanced esophageal/gastro-esophageal junction cancers and pancreatic ductal adenocarcinoma. We now have big data sets, huge sets of molecular data and clinical outcomes. We’re not smart enough, but we have machines that are using AI machine learning to say what [clinical] profile predicts what treatment we should give,” Marshall said.

“By using this profiling, I can tell you that you’re better with this one [drug] than this one. It’s going to make us smarter. So in this confusing world of oncology, where we have multiple choices and lines of therapy, my hope is that this AI technology will, in fact, make us smarter.”

**REFERENCES**


**Off Our Chests — A Candid Tour Through the World of Cancer** will be released in hardcover format on April 6, 2021.

To preorder, scan the QR code or visit, amzn.to/30dkBGN

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OncLive On Air™ is a podcast from OncLive®, which provides oncology professionals with the resources and information they need to provide the best patient care. In both digital and print formats, OncLive® covers every angle of oncology practice, from new technology to treatment advances to important regulatory decisions.

TUNE IN!

In our exclusive interview, Dr Choueiri provides perspective on the FDA approval of frontline nivolumab and cabozantinib in advanced renal cell carcinoma.
Enfortumab Vedotin Demonstrates Superiority Over Chemotherapy in Advanced Urothelial Carcinoma

by LISA ASTOR

DATA FROM THE PRIMARY ANALYSIS of the phase 3 EV-301 trial (NCT03474107) showed that enfortumab vedotin-ejfv (Padcev) had superior efficacy over chemotherapy when used in patients with advanced urothelial carcinoma who had received prior platinum-based chemotherapy and PD-1/PD-L1 inhibition. The data were presented during the 2021 Genitourinary Cancers Symposium and published simultaneously in the New England Journal of Medicine.1,2

Investigators observed benefit in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) with enfortumab vedotin (TABLE1).

The median OS with enfortumab vedotin was 12.88 months (95% CI, 10.58-15.21) versus 8.97 months (95% CI, 8.05-10.74) with chemotherapy (HR, 0.70; 95% CI, 0.56-0.89; P = .00142). Thomas Powles, MBBS, MRCP, MD, commented in a presentation during the meeting that the Kaplan-Meier curves for OS “go apart and stay apart, and the data look impressive, in my opinion.”

Subgroup analyses for OS favored the enfortumab vedotin arm for all groups except female patients (HR, 1.17), although Powles noted that some of the subgroups were too small to draw conclusions.

Median PFS with enfortumab vedotin was 5.55 months (95% CI, 5.32-5.82) versus 3.71 months (95% CI, 3.52-3.94) with chemotherapy (HR, 0.62; 95% CI, 0.51-0.75; P < .00001).

The confirmed ORR for the 301 patients treated in the enfortumab vedotin arm was 40.6% (95% CI, 34.9%-46.5%), which included complete responses in 4.9% of patients. The disease control rate (DCR) was 71.9% (95% CI, 66.3%-77.0%). In the chemotherapy arm (n = 307), the ORR was 17.9% (95% CI, 13.7%-22.8%) with complete responses in 2.7%, and a DCR of 53.4% (95% CI, 47.5%-59.2%; P < .001).

“Enfortumab vedotin is the first drug beyond chemotherapy and immunotherapy to show a significant survival advantage in previously treated advanced urothelial cancer,” Powles said. “This is a big step in the right direction for patients with advanced urothelial cancer, where treatment options remain quite limited.” Powles is a professor of genitourinary oncology, director of the Barts Cancer Centre, and lead for solid tumor research at the Barts Cancer Institute in London, England.

The Nectin-4–directed antibody-drug conjugate was granted an accelerated approval by the FDA in December 2019 for the treatment of adult patients with locally advanced or urothelial cancer who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy.3 The accelerated approval fulfills an unmet need for patients whose urothelial cancer has progressed on both chemotherapy and immunotherapy.

EV-301 served as a confirmatory trial for the benefit of enfortumab vedotin over chemotherapy in this setting, and Seagen Inc and Astellas Pharma Inc, the agent’s codevelopers, have submitted a supplemental biologics application to the FDA for regular approval.4

A total of 608 patients with histologically or cytologically confirmed urothelial cancer, including patients with squamous differentiation or mixed cell types, were enrolled in the study and randomized 1:1 with stratification to either the enfortumab vedotin arm or the chemotherapy arm. Eligible patients had radiographic progression or relapse during
or after immune checkpoint inhibition for the treatment of advanced urothelial cancer and had received prior platinum-containing chemotherapy; patients also had an ECOG performance status of 0 or 1. Stratification variables included ECOG performance status (0 or 1), region of the world, and the presence or absence of liver metastasis.

In the investigational arm, enfortumab vedotin was administered at 1.25 mg/kg on days 1, 8, and 15 of every 28-day cycle. Chemotherapy in the control arm consisted of docetaxel at 75 mg/m², paclitaxel at 175 mg/m², or vinflunine 320 mg/m² each given on day 1 of every 21-day cycle.

OS was the primary end point of the study and secondary end points included PFS, ORR, and DCR—all assessed by the investigator per RECIST v1.1 criteria—and safety.

As of the data cutoff, 81% of patients had discontinued treatment in the enfortumab vedotin arm versus 93% in the chemotherapy arm, which was due to progressive disease in 59% of patients in both arms. At a median follow-up of 11.1 months, the median treatment exposure was 5.0 months (range, 0.5-19.4) in the enfortumab vedotin arm and 3.5 months (range, 0.2-15.0) in the chemotherapy arm.

Treatment-related adverse event (TRAE) rates were similar between the 2 arms, with all grade-TRAEs occurring in 94% of the investigational arm and 92% of the control arm, and grade 3 or higher TRAE rates of 51% and 50%, respectively. Serious TRAEs were reported in 23% of patients in each arm and TRAEs led to treatment discontinuation in 14% of patients in the enfortumab vedotin arm and 11% in the chemotherapy arm.

Powles explained that the rate of grade 3 or higher maculopapular rash was increased in the enfortumab vedotin arm (7% vs 0%), whereas rates of grade 3 or higher neutrophil count decrease (6% vs 13%), white blood cell count decrease (1% vs 7%), and febrile neutropenia (1% vs 6%) were all higher in the chemotherapy arm.

TRAEs of special interest in the enfortumab vedotin arm included skin reactions of rash (all grade, 44%; grade ≥ 3, 15%) and severe cutaneous adverse reactions (all grade, 20%; grade ≥ 3, 5%), peripheral neuropathy in terms of sensory events (all grade, 44%; grade ≥ 3, 4%) and motor events (all grade, 7%; grade ≥ 3, 2%), and hyperglycemia (all grade, 6%; grade ≥ 3, 4%). The majority of TRAEs of special interest were mild to moderate in severity.

### REFERENCES

### Fast Facts

- **Enfortumab vedotin-ejfv** (Padcev) is an antibody-drug conjugate directed at Nectin-4 and is comprised of a fully human monoclonal antibody and the microtubule-disrupting agent, monomethyl auristatin E.
- **Nectin-4** is highly expressed in urothelial cancer.
- **EV-301** trial (NCT03474107) was designed to confirm the benefit of enfortumab vedotin after platinum-based chemotherapy and a PD-1/PD-L1 inhibitor.
- Seagen Inc and Astellas Pharma Inc, the agent’s codevelopers, have submitted a supplemental biologics application to the FDA for regular approval.
Adjuvant Nivolumab Improves DFS in Patients With MIUC

by DENISE MYSHKO

PATIENTS WITH MUSCLE-INVASIVE urothelial carcinoma (MIUC) who received nivolumab (Opdivo) following surgery experienced extended disease-free survival (DFS), according to results from the phase 3 CheckMate 274 trial presented at the 2021 Genitourinary Cancers Symposium.

Investigators found that adjuvant nivolumab conferred a median DFS benefit in both the intention-to-treat (ITT) and PD-L1-positive populations. In the ITT population, DFS in those treated with nivolumab (n = 353) was 21.0 months, compared with 10.9 months with placebo (n = 356; HR, 0.70; 95% CI, 0.54-0.89; \( P < .001 \)).

“This corresponds to a 47% reduction in the risk of disease recurrence or death with nivolumab,” said lead author Dean F. Bajorin, MD, a 2020 Giants of Cancer Care® award winner in Genitourinary Cancer and the Frederick R. Adler Senior Faculty Chair at Memorial Sloan Kettering Cancer Center in New York, New York. “The median DFS is nearly double with nivolumab compared to placebo.”

In the PD-L1-positive population, the median DFS in those treated with nivolumab (n = 140) was not reached, compared with 10.8 months in the placebo arm (n = 142; HR, 0.53; 98.87% CI, 0.34-0.84; \( P < .001 \)). “This corresponds to a 47% reduction in the risk of disease recurrence or death with nivolumab,” Bajorin said.

A subgroup analysis of the ITT population found no differences related to age, sex, region, or performance status, he added.

The monoclonal antibody also improved median non-urothelial tract recurrence-free survival (NUTRFS), a secondary end point of the study, as well as distant metastasis free survival (DMFS), an exploratory end point, in both the ITT and the PD-L1-positive patient populations.

In the ITT population, those treated with nivolumab experienced NUTRFS of 24.6 months versus 13.7 months in the placebo group (HR, 0.72; 95% CI, 0.58-0.89). In the PD-L1-positive population, NUTRFS in those treated with nivolumab was not reached versus 10.9 months in the placebo group (HR, 0.54; 95% CI, 0.38-0.77).

“Nivolumab is the first systemic immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in outcomes when administered as adjuvant therapy to patients with muscle-invasive urothelial carcinoma,” Bajorin said. “These results support nivolumab monotherapy as a new standard of care in the adjuvant setting for patients with high-risk MIUC after radical surgery regardless of PD-L1 status and prior neoadjuvant chemotherapy.”

The randomized, double-blind CheckMate 274 (NCT02632409) study evaluated the efficacy and safety of adjuvant nivolumab versus placebo in patients with high-risk MIUC after radical surgery. Patients were randomized 1:1 to receive nivolumab 240 mg administered once every 2 weeks or placebo for up to 1 year of adjuvant treatment. Eligible patients had radical surgery within 120 days with or without neoadjuvant cisplatin or were ineligible/declined cisplatin-based chemotherapy and were disease-free as evidenced by imaging. The primary end point of the study was DFS in the ITT population and in patients with tumor PD-L1 expression of at least 1%.

The median follow-up was 20.9 months for nivolumab 240 mg administered once every 2 weeks or placebo. In the nivolumab arm, 53.3% of patients discontinued treatment and in the placebo arm, the tumor of origin was urinary bladder carcinoma in 78.9% of patients and upper tract disease in 21% of patients. In the placebo arm, the tumor of origin was urinary bladder carcinoma in 78.9% of patients and upper tract disease in 21.1% of patients. About 40% patients in both arms were PD-L1 positive and about 43% had received prior cisplatin-based neoadjuvant chemotherapy.

The safety of nivolumab was consistent with previously reported studies in patients with solid tumors. Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 17.9% of patients in the nivolumab arm and 7.2% of patients in the placebo arm. Any-grade TRAEs leading to discontinuation occurred in 12.8% in the nivolumab arm and 2% of patients in the placebo arm. The most common TRAEs in the nivolumab arm were pruritus, fatigue, diarrhea, and rash.

Nivolumab is approved by the FDA as a monotherapy for the treatment of patients with platinum-resistant urothelial carcinoma.

REFERENCE

MORE ON OncLive.com

OncLive News Network® Features Experts From GU Conference
Live coverage from the virtual 2021 Genitourinary (GU) Cancers Symposium included daily recaps of research findings involving a broad range of tumor types. Joining OncLive’s Gina Mauro on camera were William K. Oh, MD; Julie N. Graff, MD; Bradley McGregor, MD; David A. Braun, MD; Robert J. Motzer, MD; Petros Grivas, MD, PhD; and Arlene O. Siefker-Radtke, MD.

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36 Vol. 22 | No. 06 | MARCH 2021
For women with HR+, HER2- MBC* who have visceral disease† or primary ET resistance‡

Survival doesn’t have to be at higher risk

Indication
Verzenio® (abemaciclib) is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced or metastatic breast cancer (MBC): 6

- In combination with fulvestrant for women with disease progression following endocrine therapy

Important Safety Information
Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 13% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Verzenio is the only CDK4 & 6 inhibitor to achieve significant overall survival improvement in combination with fulvestrant regardless of menopausal status\(^1,9\)

**OS in ITT Population\(^1,6\)**

- Results are based on a prespecified interim analysis and are considered definitive\(^1,10\).
- The percentage of deaths at the time of analysis was 47.3% (n=211) and 57.0% (n=127) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively\(^1,10\).
- Primary endpoint of median PFS was met: 16.4 months (95% CI: 14.4-19.3) median PFS with Verzenio plus fulvestrant vs 9.3 months (95% CI: 7.4-12.7) with fulvestrant alone (HR=0.553; 95% CI: 0.449-0.681; \(P<0.0001\))\(^6\).
- The percentage of PFS events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively\(^6\).

**Study Design**

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2- MBC who progressed on or after ET. Pre/perimenopausal women (17%) were rendered postmenopausal prior to the study. Patients had received no chemotherapy and no more than 1 prior ET in the metastatic setting. Patients were randomized 2:1 to Verzenio plus fulvestrant (n=446) or placebo plus fulvestrant (n=223). Verzenio and placebo were dosed PO BID on a continuous dosing schedule until disease progression or unacceptable toxicity. 500 mg fulvestrant was administered by IM injection on days 1, 15, and 29 of the first month and once monthly thereafter. The primary endpoint was PFS. Key secondary endpoints were ORR, OS, and DoR\(^6,8\).

**Important Safety Information (cont’d)**

**Neutropenia** occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade \(\geq 3\) decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade \(\geq 3\) neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade \(\geq 3\) neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days. Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.
In HR+, HER2- MBC*  

Even women with worse prognoses achieved survival outcomes consistent with the overall study population¹

**WOMEN WITH VISCERAL DISEASE† HAD**

8.1 months longer mOS¹  
40.3 months mOS with Verzenio plus fulvestrant (n=245) vs 32.2 months mOS with fulvestrant alone (n=128).

HR=0.675 (95% CI: 0.511-0.891)

**WOMEN WITH PRIMARY ET RESISTANCE‡ HAD**

7.2 months longer mOS¹  
38.7 months mOS with Verzenio plus fulvestrant (n=112) vs 31.5 months mOS with fulvestrant alone (n=60).

HR=0.686 (95% CI: 0.451-1.043)

• Preplanned subgroup analyses of PFS and OS were performed for stratification factors of disease site (including visceral disease) and endocrine resistance (including primary ET resistance). Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups.¹

*With disease progression following ET.  
†Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement.⁵  
‡Primary resistance was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC.⁶,⁷

**Important Safety Information (cont’d)**

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.

Grade ≥3 increases in alanine aminotransferase (ALT) (6% versus 2%) and aspartate aminotransferase (AST) (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 2.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential hepatotoxicity, monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo.

In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause fetal harm when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The most common adverse reactions (all grades, ≥10%) observed in MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 2 were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. Co-administration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced efficacy.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to one daily. The pharmacokinetics of Verzenio in patients with severe renal impairment (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis is unknown. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30–89 mL/min).

Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.
VERZENIO® (abemaciclib) tablets, for oral use

INDICATIONS AND USAGE
VERZENIO® (abemaciclib) is indicated:
- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

CONTRAINDICATIONS:
None.

WARNINGS AND PRECAUTIONS
Diarrhea
Diarrhea occurred in 81% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 90% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of VERZENIO dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further reductions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to ≤Grade 1, and then resume VERZENIO at the next lower dose.

Neutropenia
Neutropenia occurred in 41% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days. Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Fibrile neutropenia has been reported in <1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, or fatal lung disease (ILD) and/or pneumonitis can occur in patients treated with VERZENIO and other CDK 4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of VERZENIO-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended for patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue VERZENIO in all patients with Grade 3 or 4 ILD or pneumonitis.

Hepatotoxicity
In MONARCH 3, Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Monitor liver function tests (LFTs) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous Thromboembolism
In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity
Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at matenal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose.

ADVERSE REACTIONS
Clinical Studies 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.

MONARCH 2: VERZENIO in Combination with Fulvestrant
Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant-treated patients versus 10 cases (5%) of placebo plus fulvestrant-treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to thrombosis.

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 3). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, and anemia.
Table 1: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>VERZENIO plus Fulvestrant N=441</th>
<th>Placebo plus Fulvestrant N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3 %</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>86</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal Pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Anemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Leukopenia&lt;sup&gt;e&lt;/sup&gt;</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase Increased</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Aspartate aminotransferase Increased</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.
<sup>b</sup>Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.
<sup>c</sup>Includes neutropenia, neutrophil count decreased.
<sup>d</sup>Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
<sup>e</sup>Includes leukopenia, white blood cell count decreased.
<sup>f</sup>Includes platelet count decreased, thrombocytopenia.
<sup>g</sup>Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 2: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>VERZENIO plus Fulvestrant N=441</th>
<th>Placebo plus Fulvestrant N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3 %</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>90</td>
<td>23</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>87</td>
<td>29</td>
</tr>
<tr>
<td>Anemia</td>
<td>84</td>
<td>3</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>63</td>
<td>12</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>53</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>37</td>
<td>4</td>
</tr>
</tbody>
</table>

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

Drug Interactions

Effect of Other Drugs on VERZENIO

CYP3A Inhibitors

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.

Moderate CYP3A Inhibitors

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements, if necessary.

Strong and Moderate CYP3A Inducers

Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

Use in Specific Populations

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses >4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.
Pediatric Use
The safety and effectiveness of VERZENIO have not been established in pediatric patients.

Geriatric Use
Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment
No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment
No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

OVERDOSAGE
There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.

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

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AL HCP BS_M2 28JAN2020
Study Supports First-Line Immunotherapy in Non-Clear Cell RCC

by KRISTI ROSA

FIRST-LINE TREATMENT WITH immune checkpoint inhibitor–based regimens could be linked to an improvement in overall survival (OS) versus select targeted therapies in patients with metastatic non-clear cell renal cell carcinoma (RCC).

Results of a retrospective study presented during the 2021 Genitourinary Cancers Symposium showed that among 1181 patients with metastatic RCC, the median OS in those who received an immune checkpoint inhibitor–based regimen was 28.6 months (95% CI, 17.4-not reached) versus 19.2 months (95% CI, 16.7-21.9) with a VEGF inhibitor and 12.6 months (95% CI, 10.3-14.5) with an mTOR inhibitor (TABLE).

Moreover, the median time-to-treatment failure (TTF) in those who received an immunotherapy-based regimen was also longer at 6.9 months (95% CI, 2.8-14.0), compared with 5.1 months with a VEGF inhibitor (95% CI, 4.6-5.7) and 3.9 months (95% CI, 3.0-5.1) with an mTOR inhibitor.

The objective response rate (ORR) achieved in those who received an immunotherapy-based regimen (n = 65) was 25%; it was 17.8% in those who received VEGF-targeted therapy (n = 924) and 5.8% in those who received mTOR-targeted treatment (n = 186; P = .001).

“Immune checkpoint inhibitor–based frontline therapy appears to be associated with improved OS compared to VEGF and mTOR targeted therapy in patients with treatment-naive, metastatic non–clear cell RCC, even after adjustment for International Metastatic RCC Database Consortium [IMDC] risk, histology, and age,” lead study author Jeffrey Graham, MD, and colleagues, wrote in a poster on the data. Graham is an assistant professor in the Department of Internal Medicine, Section of Haematology/Oncology, at the University of Manitoba, Canada.

Immunotherapy options have induced impressive activity in patients with metastatic clear cell RCC; as such, these options have become part of standard frontline treatment. Although non–clear cell RCC represents about 15% of all kidney cancers, findings supporting the efficacy of immune checkpoint inhibitors up front have remained largely limited.

In a retrospective analysis of the IMDC, investigators included all patients who had non–clear cell histology. Patients were categorized into 3 groups based on first-line treatment: single-agent VEGF therapy, single-agent or combination immunotherapy, and single-agent mTOR therapy.

The median age of the entire patient population was 60.6 years, 65.4% were male, 76.4% had undergone nephrectomy, and 16.6% had sarcomatoid features. The most common histologic subtype across the groups was papillary disease (54.2%), and most patients fell into the intermediate IMDC risk group (55.1%). Overall, 25.1% had liver metastases, 34.2% had bone metastases, and 3.6% had brain metastases.

Of the 1181 patients included in the analysis, 78.2% had received VEGF treatment (n = 924), which included sunitinib (Sutent; n = 632; 68.4%), pazopanib (Votrient; n = 171; 18.5%), sorafenib (Nexavar; n = 72; 7.8%), cabozantinib (Cabometyx; n = 12; 1.3%), or other (n = 37; 4%). Moreover, 15.8% had received mTOR inhibitors (n = 186) in the frontline setting, such as temsirolimus (Torisel; n = 141; 75.8%) or everolimus (Afinitor; n = 45; 24.2%).

The remaining 5.5% had received immune checkpoint inhibitor–based therapy (n = 65), which could include nivolumab (Opdivo) and ipilimumab (Yervoy; n = 20; 30.8%), atezolizumab (Tecentriq) plus bevacizumab (Avastin; n = 14; 21.5%), single-agent nivolumab (n = 13; 20.0%), pembrolizumab (Keytruda; n = 13; 20.0%), or other (n = 5; 7.7%).

An analysis revealed that the hazard ratio for OS between immune checkpoint inhibitor–based therapy and VEGF treatment was 0.58 (95% CI, 0.35-0.94; P = .03), while it was 0.48 (95% CI, 0.29-0.80; P = .005) for immunotherapy-based treatment versus mTOR therapy.

TABLE. Real-world Effectiveness of First-line Therapies in Metastatic Non–Clear Cell RCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VEGF-targeted therapy (n = 924)</th>
<th>mTOR-targeted therapy (n = 186)</th>
<th>ICI-based therapy (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>19.2 (16.7-21.9)</td>
<td>12.6 (10.3-14.5)</td>
<td>28.6 (17.4-NR)</td>
</tr>
<tr>
<td>Median TTF, months (95% CI)</td>
<td>5.1 (4.6-5.7)</td>
<td>3.9 (3.0-5.1)</td>
<td>6.9 (2.8-14.0)</td>
</tr>
<tr>
<td>ORR by subgroup analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire population</td>
<td>VEGF targeted therapy (n = 924)</td>
<td>mTOR targeted therapy (n = 186)</td>
<td>ICI-based therapy (n = 65)</td>
</tr>
<tr>
<td>ORR</td>
<td>17.8%</td>
<td>5.8%</td>
<td>25%</td>
</tr>
<tr>
<td>Papillary</td>
<td>VEGF targeted therapy (n = 452)</td>
<td>mTOR targeted therapy (n = 112)</td>
<td>ICI-based therapy (n = 28)</td>
</tr>
<tr>
<td>ORR</td>
<td>13.0%</td>
<td>3.7%</td>
<td>31.6%</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>VEGF targeted therapy (n = 115)</td>
<td>mTOR targeted therapy (n = 27)</td>
<td>ICI-based therapy (n = 12)</td>
</tr>
<tr>
<td>ORR</td>
<td>20.6%</td>
<td>13.6%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>VEGF targeted therapy (n = 168)</td>
<td>mTOR targeted therapy (n = 25)</td>
<td>ICI-based therapy (n = 16)</td>
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<tr>
<td>ORR</td>
<td>15.2%</td>
<td>0%</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; RCC, renal cell carcinoma; TTF, time-to-treatment failure.

REFERENCE

Apalutamide Shows Sustained Survival Benefit in mCSPC

by BENJAMIN SAYLOR

TREATMENT WITH APALUTAMIDE

(Erleada) plus androgen-deprivation therapy (ADT) reduced the risk of death by 35% versus ADT alone in patients with metastatic castration-sensitive prostate cancer (mCSPC), according to results of the final analysis of the phase 3 TITAN trial (NCT02489318) presented at the 2021 Genitourinary Cancers Symposium.1

In the randomized, double-blind, placebo-controlled TITAN trial, 1052 patients with mCSPC were randomized 1:1 to receive apalutamide plus ADT (n = 527) or placebo plus ADT (n = 525). Dual primary end points were radiographic progression-free survival (rPFS) and overall survival (OS), according to investigator Kim N. Chi, MD, chief medical officer and vice president of BC Cancer, Vancouver, Canada.

Findings from the primary analysis of the trial were published in 2019. At a median follow-up of 22.7 months, both rPFS and OS reached statistical significance, according to Chi. The 2-year OS rates at the primary analysis were 82.4% in the apalutamide arm versus 73.5% in the control arm, translating to a 33% reduction in the risk of death (HR, 0.67; P = .005). Based on the primary TITAN analysis, the FDA approved apalutamide in September 2019 for the treatment of patients with mCSPC.

The primary TITAN analysis served as the final analysis for rPFS and first interim analysis for OS. Upon recommendation of the independent data monitoring committee, the trial was unblinded and 39.5% of patients in the placebo group who had not progressed went on to receive open-label apalutamide (n = 208).

Final analysis of the TITAN trial occurred at a median follow-up of 44.0 months. A total of 405 OS events had occurred. The median duration of treatment in the apalutamide plus ADT, crossover apalutamide plus ADT, and placebo plus ADT groups was 39.3 months, 20.2 months, and 15.4 months, respectively.

With longer follow-up, treatment with apalutamide plus ADT reduced the risk of death by 35% (HR, 0.65; 95% CI, 0.53-0.79; P < .0001). After adjusting for crossover using a preplanned sensitivity analysis, investigators found a 48% reduction in the risk of death (HR, 0.52; 95% CI, 0.42-0.64; P < .0001).

The treatment effect on OS was found to favor apalutamide plus ADT across all prespecified subgroups except for patients who had received prior docetaxel. “However, this subgroup comprised only 10% of patients, and among them, there have been relatively few events,” Chi said. “A post hoc interaction analysis between treatment and prior use of docetaxel showed no significant interaction.”

Other clinically relevant end points, including second PFS (PFS2) and time to castration resistance, also favored apalutamide plus ADT.

Specifically, the median PFS2 for patients in the apalutamide plus ADT arm was not reached, versus 44.0 months in the placebo arm (HR, 0.62; 95% CI, 0.51-0.75; P < .0001). The median time to castration resistance was not reached with apalutamide plus ADT compared with 11.4 months with ADT and placebo (HR, 0.34; 95% CI, 0.29-0.41; P < .0001).

PFS2 was defined as the time from randomization to the first occurrence of investigator-determined disease progression on first subsequent therapy or death. The second, time to castration resistance, was defined as time from randomization to radiographic disease progression, prostate-specific antigen progression, or symptomatic skeletal event, whichever occurred first.

Health-related quality of life (HRQOL) was measured using the Functional Assessment of Cancer Therapy-Frostate total score. Chi reported that HRQOL was maintained in the treatment group, with no difference between the treatment and placebo groups.

The safety profile of apalutamide plus ADT was found to be consistent with previous reports, according to Chi. “Importantly, cumulative incidence of any-grade treatment-emergent falls, fractures, and fatigue was similar between groups. The cumulative incidence of grade 3/4 treatment-emergent adverse events and serious adverse events were also similar between groups. As expected, the incidence of any-grade rash was higher in the apalutamide group than in the placebo group [29.2% vs 9.3%], but reached a plateau after about 6 months,” Chi said.

REFERENCES


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Analysis Confirms Atezolizumab Benefit for PD-L1–positive mUC

Atezolizumab (Tecentriq) monotherapy demonstrated a trend toward a median overall survival benefit over the chemotherapy doublet of platinum-based therapy plus gemcitabine in cisplatin-ineligible patients with PD-L1–high metastatic urothelial carcinoma (mUC), according to findings from an exploratory analysis of the phase 3 IMvigor210 study (NCT02807636).

Matthew D. Galsky, MD, professor of medicine and acting chief of the Division of Hematology and Medical Oncology at the Mount Sinai Icahn School of Medicine in New York, New York, presented the latest results at the 2021 Genitourinary Cancers Symposium.
**Clinical Trial In Focus**

**Pancreatic Cancer**

**Study Tests Guidelines for Monitoring Pancreatic Cysts**

*by Denise Myskho*

**Investigators Are Seeking To** determine the optimal protocol for monitoring patients with pancreatic cysts to better identify neoplasms that are more likely to become malignant. The ECOG-ACRIN Cancer Research Group is aiming to recruit approximately 4600 people for a long-term study comparing a low- with a high-intensity surveillance approach in the EA2185 trial (NCT04239573).1

Pancreatic cysts are very common findings in otherwise healthy patients as they get older, said David S. Weinberg, MD, MSc, principal investigator on the study. Although cysts have been identified in up to 20% of patients undergoing MRI, the risk of progression to pancreatic cancer varies depending upon clinical and radiographic features.2,3 In surgical studies, the incidence of malignancy ranged from 15% to 25% for certain ductal neoplasms to 0.25% for low-risks cysts.3

“A minority [of cysts] have the potential to turn into cancer,” said Weinberg, who is the chief of the Section of Gastroenterology, and Audrey Weg Schaus and Geoffrey Alan Weg Chair in Medical Science at Fox Chase Cancer Center in Philadelphia, Pennsylvania. “We just don’t know on the day of their identification which ones might and which ones might not.”

Patients with pancreatic cysts are managed with surveillance protocols, but at present there is no consensus on which protocol is the most clinically effective or which is the best use of resources. The 2 major strategies for the management of pancreatic cysts are detailed in the Fukuoka guideline, published initially in 2012 and revised in 2017,4 and the American Gastroenterological Association (AGA) recommendations, published in 2015.5 Significant differences exist between the 2 approaches, with the updated Fukuoka guidelines being the more intensive monitoring program.6

Both guidelines are clinically accepted, and insurance companies cover the costs of monitoring, Weinberg said. “The problem is that nobody knows which one works better or which one adds the most value. Guidelines are supposed to reduce variation in health care because they take the best evidence and make recommendations for providers on how to take care of patients. Competing guidelines sow confusion.”

The Fukuoka surveillance guidelines recommend an MRI or a CT scan at 6 months for cysts less than 1 cm and then every 2 years if there is no change. For cysts that are 1 cm to 2 cm, MRI or CT should be conducted annually, then every 2 years if the cyst is stable. For cysts 2 cm to 3 cm, an endoscopic ultrasound (EUS) is recommended at months 3 to 6; after that, the EUS and MRI can alternate, and the time between scans can be lengthened. For cysts greater than 3 cm, the guideline recommends alternating between MRI and EUS every 3 to 6 months.4

In the Fukuoka guidelines, surgery is recommended if the EUS reveals main duct features that are suspicious or cytology that is suspicious or positive for malignancy. The guidelines also recommend that resection be considered for cysts greater than...
3 cm in younger patients who would otherwise require prolonged surveillance.6

The AGA guideline recommends MRI in the first year, then every 2 years, for cysts less than 3 cm, with surveillance if there is no significant change in size or characteristics.

For cysts with higher-risk features, including size greater than 3 cm, the guideline recommends examination with an EUS with fine-needle aspiration (FNA). If these results are not suspicious, patients can undergo MRI after 1 year and then switch to every 2 years.

Patients with significant changes in the cyst are advised to undergo an EUS with FNA, and then are referred to the surgery department.5

“As you would predict, the more intensive surveillance strategy finds more cancers. It also provokes more surgery that is unnecessary or not useful,” Weinberg said. “Having surgery to remove what turns out to be a benign cyst, unfortunately, exposes patients to substantial risk.

“With all the best intentions, we are operating on a lot of people that if we knew they didn’t have cancer we wouldn’t want to operate on, and we are periodically letting patients slip through our fingers whom we might have been able to protect,” he added.

He said the Whipple procedure, or pancreaticoduodenectomy, is the most frequently performed pancreatic resection, but this is a complex surgery and is associated with serious complications. In a retrospective analysis involving 4945 patients, the rate of serious complications was 27.1%, most frequently sepsis (15.3%), surgical site infection (13.1%), and respiratory complications (9.5%). The mortality rate within 30 days was 2.6%.7

SURVEILLANCE STUDY DETAILS

The ECOG-ACRIN study will randomize patients to 1:1 to surveillance with either a low-intensity protocol modeled on the AGA guidelines or a high-intensity strategy based on the Fukuoka guidelines (FIGURE 1A). “The most salient differences between the 2 surveillance strategies center on indications for and recommended intervals of cross-sectional imaging and EUS utilization,” Weinberg and colleagues said in an article in Contemporary Clinical Trials.8

In the low-intensity arm, patients will undergo MRI or a CT scan at the beginning of the trial and again in 1 year. Participants with no abnormalities will repeat the MRI or CT every 2 years. Those with positive imaging features at 1 or 2 years will undergo an EUS. If the EUS is negative, participants will repeat the MRI or CT in 1 year.9

In the high-intensity arm, patients also will undergo MRI or CT at study entry. Those with 1-cm to 2-cm cysts will receive an MRI or CT every 6 months for 1 year, then every 12 months for 2 years, and then every 24 months thereafter. Patients with 2-cm to 3-cm cysts at baseline will undergo an EUS within 6 months; if that test is negative, they will repeat the MRI or CT in 1 year. If a second EUS is negative, patients will undergo alternate MRI or CT and EUS every 12 months. Patients with cysts larger than 3 cm will undergo EUS within 6 months, and if that is negative, they will alternate MRI or CT with EUS every 3 to 6 months.8

Participants in either arm will be recommended for surgery if they develop obstructive jaundice due to the pancreatic cyst; an enhancing nodule 5 mm or larger in the cyst wall; or main pancreatic duct dilation of 10 mm or larger.

The primary end point of the study is a comparison of unfavorable outcomes within each arm. Unfavorable outcomes are defined as any pancreatic cancer without surgery; unresectable pancreatic cancer or cancer larger than T1a, N0 at surgery; or benign disease at surgery. Favorable outcomes would be high-grade dysplasia and/or resectable, early-stage pancreatic cancer (T1a, N0) at surgery, or benign disease and no surgery.8

“For statistical reasons, the power of the study is driven by a comparison of the unfavorable outcomes across arms,” Weinberg said.

Secondary end points include clinical measures such as surgical mortality and major morbidity rates, health care resource utilization costs and metrics, and patient-reported outcomes.

The study, which is scheduled to last for 8 years, aims to enroll patients in 150 sites across the United States. Eligible patients are those with newly identified pancreatic cysts greater than 1 cm. Weinberg said investigators are exploring opening the enrollment to international sites.

The coronavirus 2019 (COVID-19) pandemic has affected enrollment efforts, Weinberg said. Health care use is low for any nonemergency service.

“This is clearly meant to be a prevention trial,” he said. “Patients are not getting the CT in the first place that shows the cyst. And even if they do get that CT that finds a pancreatic cyst, patients are asking their doctors if surveillance can wait until after they are vaccinated. At Fox Chase pre-COVID, we probably saw 3 to 5 new patients per week who would have fit the inclusion criteria for this trial. At this point, we’re probably seeing 1 patient every week or so.”

Investigators will also collect biosamples from patients over time that will be banked for possible evaluation for biomarkers. The hope, Weinberg said, is that in addition to reliably identifying the most clinically effective surveillance strategy, investigators can identify better ways to determine which cysts could become cancer.

“People are coming up with new biomarkers all the time. Hopefully, by the time this trial is over, there will be better ones, and we’ll have this treasure trove of patients (a lot of them), biosamples on most of them, and clinical outcomes on all of them to see if there are any markers that predict cancer,” he said.
FOR ADULT PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

BRUKINSA STAYS ON, SO BTK 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.1,2

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 hemoptysis 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 antplatelet 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.

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BRUKINSA—THE BTK INHIBITOR DEMONSTRATED TO PROVIDE COMPLETE AND SUSTAINED INHIBITION1,2

POWERFUL RESPONSES1

<table>
<thead>
<tr>
<th>STUDY 206</th>
<th>PET-BASED</th>
<th>STUDY 003</th>
<th>CT-BASED</th>
</tr>
</thead>
<tbody>
<tr>
<td>84% ORR</td>
<td>(95% CI: 74, 91)</td>
<td>84% ORR</td>
<td>(95% CI: 67, 95)</td>
</tr>
<tr>
<td>59% CR</td>
<td></td>
<td>22% CR</td>
<td></td>
</tr>
<tr>
<td>19.5 mo MEDIAN DOR</td>
<td>(95% CI: 16.6, NE)</td>
<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 0033

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.

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
Sacituzumab Govitecan Induces Clinical Benefit Across Biomarker Subgroups in Metastatic TNBC

by KRISTI ROSA

THE ANTIBODY-DRUG CONJUGATE (ADC)
Sacituzumab govitecan-hziy (Trodelvy) was found to induce clinical benefit over therapy of physician’s choice (TPC) in patients with metastatic triple-negative breast cancer (TNBC), irrespective of TROP2 expression, according to data from an exploratory biomarker analysis of the phase 3 ASCENT trial (NCT02574455). Notably, greater efficacy was observed in those who had a medium or high TROP2 score.¹

Results from the trial presented during the 2020 San Antonio Breast Cancer Symposium showed that the median progression-free survival (PFS) was higher in patients who received the ADC versus those who were given TPC across all subgroups for which TROP2 was analyzed. Patients who had a histochemical score of less than 100 were determined to be TROP2 low, while those with a score between 100 and 200 were TROP2 medium, and those with a score of 200 to 300 were TROP2 high.

In the TROP2-high subgroup, the median PFS in the investigative and control arms was 6.9 months versus 2.5 months, respectively, and in the TROP2-medium subgroup, median PFS was 5.6 months and 2.2 months, respectively, while in the TROP2-low subset, the median PFS was 2.7 months versus 1.6 months, respectively (TABLE¹).

Furthermore, sacituzumab govitecan also outperformed TPC with regard to median overall survival (OS) across all TROP2 subgroups. The median OS was longest in the TROP2-high subgroup compared with TPC (14.2 months vs 6.9 months, respectively) and in the TROP2-medium subgroup (14.9 months vs 6.9 months, respectively). In the TROP2-low subgroup, the median OS with the sacituzumab govitecan was 9.3 months versus 7.6 months with TPC.

“TROP2 is expressed in all breast cancer subtypes, including TNBC, and has been linked with poor prognosis and decreased survival,” said Sara A. Hurvitz, MD, associate professor at the David Geffen School of Medicine at UCLA. “TNBC has been shown to have high membrane expression of TROP2, with up to 88% of primary and metastatic tumors having moderate to strong TROP2 staining. Sacituzumab govitecan has demonstrated activity in translational models of TNBC with relatively high TROP2 expression.

“The highest efficacy outcomes were seen in sacituzumab govitecan-treated patients from the TROP2-high and TROP2-medium subgroups compared with TPC. Sacituzumab govitecan also outperformed TPC regardless of germline BRCA1/2 mutation status,” added Hurvitz, who is also medical director of the Jonsson Comprehensive Cancer Center Clinical Research Unit, codirector of the Santa Monica-UCLA Outpatient Oncology Practices, and director of the Breast Cancer Clinical Trials Program at UCLA.

BRCA mutations are detected in approximately 10% of patients with TNBC, according to Hurvitz. These mutations are known to be involved with deficiencies in homologous repair of double-stranded DNA breaks and may make cells susceptible to other agents that block such mechanisms.

“Topoisomerase I inhibitors, including SN-38, and the payload in the ADC, increase single-strand DNA breaks irrespective of BRCA mutations. Sacituzumab govitecan has demonstrated activity in BRCA-mutant translational models of TNBC and may confer synthetic lethality to TNBC tumors.”

A CLOSER LOOK AT BIOMARKER ANALYSIS
Sacituzumab govitecan is a first-in-class ADC that is highly specific for TROP2. The antibody is conjugated via a hydrolysable linker to SN-38, which represents an active metabolite of irinotecan in a high drug to antibody ratio of 7:6:1, Hurvitz explained. To release SN-38 from the antibody, internalization and enzymatic cleavage by the tumor cells are not needed. Hydrolysis of the linker liberates SN-38 extracellularly to elicit a bystander effect in patients who receive the ADC.

For the exploratory biomarker analysis, investigators set out to examine the link between efficacy and TROP2 expression or germline BRCA1/2 mutation status. To determine TROP2 expression, investigators requested primary or metastatic archival biopsy or surgical specimens at the time of study entry; however, this was not a requirement for eligibility. From these samples, TROP2 expression was examined using a validated immunohistochemistry assay; it was categorized based on histochemical score. If known, germline BRCA1/2 mutation status was collected at baseline, Hurvitz noted.

Investigators examined the link between efficacy and biomarkers in the primary population of patients who were negative.

### TABLE. Subgroup Outcomes in ASCENT Trial¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TROP2 high</th>
<th>TROP2 medium</th>
<th>TROP2 low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sacituzumab govitecan (n = 85)</td>
<td>TPC (n = 72)</td>
<td>Sacituzumab govitecan (n = 39)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.9 (5.8-7.4)</td>
<td>2.5 (1.5-2.9)</td>
<td>5.6 (2.9-8.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.2 (11.3-17.5)</td>
<td>6.9 (5.3-8.9)</td>
<td>14.9 (6.9-NE)</td>
</tr>
</tbody>
</table>

OS, overall survival; NE, not evaluable; PFS, progression-free survival; TPC, therapy of physician’s choice.
for brain metastases, and only those with known TROP2 expression or BRCA1/2 data were included in the assessment. The data cutoff for the analysis was March 11, 2020. A total of 468 patients were included in the assessment: 235 in the ADC arm and 233 in the TPC arm. TROP2 expression was known for 64% of those in the ADC arm versus 60% in the TPC arm. “More than 50% of evaluable patients in both arms had high TROP2 expression by age score,” Hurvitz said. BRCA mutation status was collected for 63% of those in the ADC arm versus 61% in the TPC arm at baseline. Only 7% to 8% of patients had BRCA1/2 positivity.

Additional results from the analysis revealed that sacituzumab govitecan also outperformed TPC in terms of objective response rate (ORR) across all TROP2 subgroups examined. “Notably, a significant difference in response rate was noted for the TROP2-high subgroup,” Hurvitz said. The ORRs with the ADC and TPC in the TROP2-high subgroup were 44% versus 1%, respectively. In the TROP2-medium subgroup, these rates were 38% versus 11%, respectively; in the TROP2-low subgroup, the ORR rates were 22% versus 6%, respectively (FIGURE). Moreover, efficacy outcomes proved to be numerically higher for the ADC versus TPC in the subgroup of patients with BRCA1/2 positivity, although this benefit did not reach statistical significance. “Due to the low patient number, however, these data should be interpreted with caution,” Hurvitz said. Sacituzumab govitecan showed a similar toxicity profile across all TROP2 subgroups examined. “This shows that TROP2 expression did not affect toxicity,” Hurvitz noted. The key grade 3 or higher treatment-associated adverse effects of special interest for the TROP2-high subgroup with the ADC versus TPC included neutropenia (47% vs 32%, respectively), diarrhea (12% vs 0%), and anemia (10% vs 5%).

AN ADC ENTERS THE TREATMENT LANDSCAPE FOR TNBC
In April 2020, based on data from a phase 1/2 trial of the agent, the FDA granted sacituzumab govitecan accelerated approval for use in adult patients with metastatic TNBC who have received at least 2 previous therapies for metastatic disease. In the trial, the ADC demonstrated an ORR of 33.3% via local assessment (95% CI, 24.6%-43.1%), and a median duration of response of 7.7 months (95% CI, 4.9-10.8) at a median follow-up of 9.7 months.

Data from ASCENT, which is the confirmatory trial of the ADC, were presented during the European Society for Medical Oncology Virtual Congress 2020 and showed that the median PFS with sacituzumab govitecan versus TPC was 5.6 months versus 1.7 months, respectively (HR, 0.41; P < .0001). Moreover, the median OS was 12.1 months versus 6.7 months (HR, 0.48; P < .0001). The ORR with the ADC was 35% versus 5% with TPC. These benefits were observed across all subgroups analyzed on the trial. A total of 529 patients with metastatic TNBC who had received at least 2 prior lines of chemotherapy for advanced disease were randomized 1:1 to receive either intravenous sacituzumab govitecan at a dose of 10 mg/kg on days 1 and 8 of every 21-day treatment cycle or TPC of single-agent chemotherapy in the form of either eribulin, vinorelbine, gemcitabine, or capecitabine. Patients were stratified based on the number of prior lines of chemotherapy received (2-3 vs > 3), geographic region (North America vs Europe), and the presence versus absence of known brain metastases (yes vs no).
Anti-HER3 Agent Shows Promise in EGFR-Mutant NSCLC

by CAROLINE SEYMOUR

THE HER3-DIRECTED antibody-drug conjugate (ADC) patritumab deruxtecan (U3-1402) continued to demonstrate clinically meaningful antitumor activity and a manageable safety profile at the recommended expansion dose of 5.6 mg/kg in pretreated patients with metastatic or unresectable EGFR-mutant non–small cell lung cancer (NSCLC). The findings from a phase 1 study (NCT03260491) were presented during the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.

As of April 30, 2020, 57 patients with EGFR-mutant NSCLC from the dose-escalation and dose-expansion portions of the trial had been treated with patritumab deruxtecan. Fifty-six patients were evaluable for response.

The confirmed objective response rate per blinded independent central review was 25% (n = 14; 95% CI, 14.4%-38.4%), which consisted of a 2% complete response rate (n = 1) and a 23% partial response rate (n = 13). The stable disease rate was 45% (n = 25).

“Early antitumor activity was observed in this heavily pretreated patient population, with a median follow-up time of 5 months,” wrote Helena A. Yu, MD, lead study author and medical oncologist, Memorial Sloan Kettering Cancer Center, and colleagues in a presentation of the data. “These data support further clinical investigation of this HER3-directed ADC in a patient population with no available targeted therapy treatments.”

HER3 is expressed in more than 80% of EGFR-mutant NSCLC and overexpression is associated with poor outcomes. Patritumab deruxtecan is a novel HER3-directed ADC that consists of the monoclonal antibody patritumab, a tetrapeptide-based linker, and a topoisomerase I inhibitor payload.

In the dose-escalation phase of the study, patients with metastatic or unresectable EGFR-mutant NSCLC who had progressed on osimertinib (Tagrisso) or were T790M negative after progression on erlotinib (Tarceva), gefitinib (Iressa), or afatinib (Gilotriff) received 5.6 mg/kg of patritumab deruxtecan every 3 weeks. The dose-expansion phase included patients with metastatic or unresectable EGFR-mutant NSCLC who had received at least 1 prior EGFR tyrosine kinase inhibitor (TKI) and at least 1 prior platinum-based chemotherapy regimen received 5.6 mg/kg of patritumab deruxtecan every 3 weeks.

Evaluation of the antitumor activity of patritumab deruxtecan served as the primary end point of the study. The safety and tolerability of the agent were evaluated as secondary end points.

Patients had received a median of 4 prior lines of therapy for advanced or metastatic disease (range, 1-9). Approximately half (n = 27; 47%) had a history of central nervous system metastases. Additional data indicated that the disease-control rate was 70% (n = 39; 95% CI, 55.9%-81.2%). The median time to response was 2.0 months (range, 1.2-2.8) and the median duration of response was 6.9 months (range, 3.0-7.0).

In terms of safety, the most common grade 3 or greater treatment-emergent adverse effects (TEAEs) were thrombocytopenia (n = 16; 28%) and neutropenia (n = 11; 19%). TEAEs associated with drug discontinuation (9%) included fatigue (n = 2), decreased appetite (n = 1), interstitial lung disease (ILD; n = 1), pneumonitis (n = 1), and upper respiratory tract infection (n = 1). No discontinuations were attributed to thrombocytopenia or neutropenia.

Investigators determined 3 (5.3%) ILD events as being related to treatment by an independent central review committee. No treatment-related AEs were associated with death.

According to an exploratory biomarker analysis, which was also presented during the conference, almost all evaluable patient tumors (n = 43) expressed membrane HER3 at baseline. The median membrane H score was 180 (range, 2-280) out of 300.

Moreover, heterogenous EGFR TKI resistance mechanisms were identified in patients’ pretreatment tumor tissue and circulating tumor DNA (ctDNA). Investigators reported clinical responses in patients with diverse TKI resistance mechanisms, including EGFR T790M mutations (53%), MET amplifications (8%), ERBB2 (HER2) mutations (4%), BRAF fusions, EGFR C797S mutations, and PIK3CA mutations.2 Other mutations included HER3 (2%), HER4 (8%), CDKN2A (6%), and NTRK2 (2%).

All examined patient samples showed a reduction in EGFR-activating mutations in ctDNA following treatment with patritumab deruxtecan. Patients who experienced a confirmed clinical response were more likely to have ctDNA clearance of EGFR-activating mutations at week 3 or week 6. Failure to clear EGFR-activating mutations in ctDNA was associated with a best overall response of progressive disease.

“These data provide important insights about how a HER3-directed therapy may interact in previously treated NSCLC tumors with diverse mechanisms of EGFR TKI resistance, including mechanisms not directly related to EGFR,” said Pasi A. Jänne, MD, PhD, in a discussion of the data. Jänne is director of the Jänne Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute. “While an association between higher levels of HER3 expression and clinical activity was seen with patritumab deruxtecan, additional analyses from this study and additional studies are needed to better understand the role of HER3 expression alone in the optimal selection of patients.”

The phase 2 HERTHENA-Lung01 study (NCT04619004) will evaluate single-agent patritumab deruxtecan in patients after failure of EGFR TKIs and platinum-based chemotherapy.

For a full list of references, see the article at bit.ly/3kYvhSB.
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City of Hope Cancer Center
Chief Medical Officer, International Myeloma Foundation

Saad Usmani, MD
Division Chief, Plasma Cell Disorders
Levine Cancer Institute – Atrium Health
The COVID-19 Pandemic Will Have Long-Term Impact on Oncology Practices

by BRUCE FEINBERG, DO

THE CORONAVIRUS-19 (COVID-19) pandemic has permeated every aspect of health care since March 2020. For oncologists, the pandemic created new patient care challenges, such as how to reduce risks of virus exposure for patients who may be immunocompromised and switching from in-person visits to telemedicine.

As much discussion has been focused on the pandemic’s effect on patients, less is understood about how it has affected health care providers and their practices. For instance, how is the COVID-19 pandemic affecting practices financially? Is it influencing their performance in value-based reimbursement?

Another area that needs to be understood is the pandemic’s effect on the level of stress oncologists face at work. Research conducted by Cardinal Health Specialty Solutions showed that oncologists have responded to the pandemic with resourcefulness and resiliency while managing higher-than-ever stress levels.

More data on the pandemic’s impact were collected by Cardinal Health using a web-based survey sent in September, October, and November 2020. The results reflect the views of more than 190 oncologists from a mix of community- and hospital-based practices across the United States.

Overall, the survey showed that the pandemic has had a far-reaching impact on oncology practices and how oncologists treat patients (FIGURE 1). For example, about half of participating oncologists said their practices have taken advantage of government-supported small business loans. Additionally, nearly half of participating oncologists said the pandemic will drive greater use of oral therapeutics for patients in the future.

In addition, clinicians have been forced to receive information about new therapies in different ways than before (FIGURE 2). Without the ability to attend medical conferences in person, 63% reported that they have been taking advantage of virtual programming, while 55% said they are relying on medical journals for data about new drugs.

TELEMEDICINE: HERE TO STAY

Of all the changes to occur because of the COVID-19 pandemic, the adoption of telemedicine might be the most significant shift, having moved from almost nonexistent use before the pandemic to a state where, at the peak of the pandemic, 97% of oncologists were using it to some degree. They are generally satisfied with the experience. Nearly 6 in 10 participating oncologists said their telemedicine experience has been highly positive or better than expected.

However, in more recent months, telemedicine usage has leveled off considerably, oncologists reported. Yet 80% of those surveyed expect to continue using it to some degree post pandemic.

Given the expectation that telemedicine is here to stay, understanding where clinicians believe it to be a safe, effective, and viable solution for ongoing disease surveillance and management is critical.

Participating oncologists said reviewing laboratory/imaging results with patients and routine monitoring of conditions were the 2 areas where telemedicine could best be used.

Survivorship care, management of maintenance therapies, and palliative care were also regarded as potentially suited to telemedicine, albeit to a lesser degree.

Along with monitoring patients, some physicians see telemedicine as a tool that can help prevent unnecessary costs.

For example, William R. Mitchell, MD, chief executive officer and senior partner, Southern Oncology Specialists in Charlotte, North Carolina, said his practice has used telemedicine as a tool for triaging patients who are considering a visit to the emergency department (ED).

“If patients call because they are experiencing an adverse event, the routine response is often to send them to the ED,” he said. “By using telemedicine, we can talk to the patients and see how they look,
which helps us to better evaluate their
condition and make more informed deci-
sions about whether they need urgent care.
Preventing those unnecessary trips to the
ER can lead to a significant reduction in
costs for patients."

Although 3 in 5 of surveyed providers
reported having a favorable experience
with telemedicine, they also addressed
remaining barriers such as technology
challenges and lack of patient adoption.

In addition, 48% said the use of telemed-
icine has had a negative financial impact
on their practice. Despite these challenges,
60% said their patients have had a favor-
able experience with telemedicine, which
bodes well for future use.

**USE OF ORAL THERAPIES**
The survey also asked oncologists about
the transition from infused therapies to
oral therapies to limit the number of office
visits since the pandemic may continue
to affect oncology practices for months.
Two-thirds of oncologists have moved
at least some patients to oral therapies,
according to the survey results.

While these changes have been driven
by a need to limit in-person appointments,
physicians were split on whether increased
use of oral therapeutics would continue
after the pandemic is over.

“When evaluating infused therapies
versus oral therapies, oncologists need
to consider many factors,” Mitchell said.
“First and foremost is the well-being of the
patient. Infused therapies allow for more
direct monitoring of the patient, as well
as better adherence to treatment, which
can lead to better outcomes. Another factor
is the impact on the practice. Shifting
a large portion of patients to oral thera-
pies may create operational and financial
challenges for many community prac-
tices, particularly those that don’t have an
in-house pharmacy.”

The challenges of the pandemic have
also led to the idea of home care or home
infusion services, which about 1 in 3
surveyed oncologists said their practices
are offering or considering. This comes
with barriers, including staff and resource
limitations, patient safety concerns, and
payer restrictions.

**FINANCIAL IMPACTS SEEN
AS SHORT TERM**
The COVID-19 pandemic has also taken
a financial toll on practices throughout
the country. Ninety percent of surveyed
oncologists acknowledged some negative
impact. However, nearly 70% said these
challenges are only short term, and more
than 70% believe they are very confident
or confident their practices will return to
pre-pandemic levels of success and profit-
ability as COVID-19 wanes.

Nearly half of the participating oncologists
have tapped into government-supported
loans such as the Coronavirus Aid, Relief,
and Economic Security (CARES) Act, in
which the Department of Health and Human
Services offered financial relief to providers
who bill Medicare fee-for-service. In addi-
tion, 40% are limiting investments in the
practice, and a third are planning to delay
any investment by 1 year or more.

Of those participating in value-based
care initiatives such as Merit-based
Incentive Payment Systems (MIPS) and the
Oncology Care Model (OCM), two-thirds
say the pandemic has had no negative
effect on their performance. However,
more than 50% of respondents expect
value-based care initiatives will be signifi-
cantly delayed or shelved as a consequence
of the pandemic.

**INCREASING BURNOUT**
All of these COVID-19-influenced factors
can affect oncologists in personal ways,
too. Research conducted prior to the
pandemic indicated that oncologists were
already at higher risk of burnout than
providers in other specialties.

Interestingly, the increased feelings of
burnout since the pandemic began were
not related to a heavier workload. Instead,
loss of face-to-face patient interactions
was cited as the top factor contributing to
physician burnout.

Reduced patient volumes and practice
financial loss were also commonly cited.
This finding suggests that, while tools like
telemedicine may continue to play a role in
care, in-person patient care is what drives
most oncologists.

“Oncologists get very close to their
patients. It is almost like a family
relationship,” Mitchell said. “Just as families have been stressed by not being able to spend time together during the pandemic, the inability to connect with patients face-to-face has created added stress for many oncologists.”

Barriers across community-based oncology practices remain an all-too-real challenge as the COVID-19 pandemic continues.

With vaccinations rolling out across the country, though, there is hope that oncology practices will enjoy renewed success sooner rather than later, and the measures adopted in response to the pandemic may yield lasting improvements to benefit both patients and clinicians.

Bruce Feinberg, DO, is vice president and chief medical officer at Cardinal Health Specialty Solutions.

REFERENCE

How Health Care Practices Can Stay Viable During and After COVID-19

by KEITH A. REYNOLDS

AIMEE GREETER, SENIOR VICE PRESIDENT of Coker Group, a health care consultant in Alpharetta, Georgia, spoke about ways to stay ahead of the coronavirus-19 (COVID-19) pandemic and what practices can take away from it to offer better care in the future.

Q: What is the current state of health care?
A: I would say that the health care industry’s current state is one of adaptivity. So, we are having to be fluid in our actions, in our decisions, and in our communications right now. Because things are changing very, very rapidly, and we have to adapt to it.

Q: In the next 1 to 2 years, what do you see as the biggest challenge for practices?
A: This is really the crystal ball question. I can appreciate that, but I don’t know that I have all the answers. There are challenges facing practices in the next 6 months, 1 year, 2 years. Some trends that we’re starting to see indicate that patients aren’t that excited about coming back for things that we would have normally considered to be emergent or urgent cases. And so, as people struggle to find the competence to return to their physician practices, I think we’re going to have to work really hard to get them back to a level of comfort over the [months and years to come].

Q: What can a practice leader do to keep their practice viable during the pandemic?
A: We are seeing questions about reimbursement for telehealth that are starting to percolate. People have made a big switch and invested, in some cases heavily, in technology that they’ve never had before on the assumption that there is going to be lasting reimbursement. And is that really going to be the case going forward? I know that there’s a lot of discussions, and lobbyists on Capitol Hill are pushing for that to continue. We also need to ask these questions: What is the physical plan of a practice going to look like going forward? Even if we move [some patients] to telehealth, does that mean that we still need as much space for our physician practices as previously? We’re starting to see people scale back on their plans for owning or investing in real estate.

Q: Is there anything you would like to see continue into the post-COVID-19 world?
A: The sense of patient-centeredness that we’ve been having recently, and part of that is our opportunity to respond to patient needs. I like thinking about what our patients need before they even walk in our door and giving them the resources that they need to get them comfortable with what services they’re procuring at that time. I think if we put ourselves in that position to think about what’s easiest for patients, what’s best for patients, what’s cheapest, in some cases, for patients; that’s going to help lead us to future success. We really need to center ourselves.

Q: Do you have any final thoughts on the pandemic and its impact on the health care industry?
A: Some of the thought leadership that’s come out has talked about the double shift, people who work all day and then have families that they need to take care of in the evenings. Be gentle with yourselves, and be gentle with other leaders, because there are so many things going on in people’s lives right now. A little bit of compassion and kindness can go a long way. It differentiates us as people and as leaders. I think it’ll be really impactful during this time and, hopefully, that could be a trend that we could continue to see into the future.

This interview has been edited for clarity and length.
BETTER IS HOME TO NEW JERSEY’S BEST CANCER CENTER

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

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
Surgical Intervention Provides the Foundation for Exploring Immunotherapy in Glioblastoma

by MAHUA DEY, MD

EVEN AFTER THE MOST AGGRESSIVE standard-of-care multimodal treatment strategy—radiation, combining maximal safe resection with temozolomide chemotherapy, and tumor treatment fields—the median overall survival (OS) for patients with glioblastoma (GBM), the most common adult primary brain tumor, is only 20.9 months. Numerous biological and clinical features affect survival outcomes for patients with GBM tumors; these include IDH1/2 mutations, MGMT promoter methylation, 1p/19q chromosomal arm deletions, and the absence of TERT mutations, as well as certain patient characteristics such as age, extent of surgical resection, and performance score. In addition, study results indicate that participation in clinical trials is associated with better response to standard-of-care treatment in this patient population.2

However, even patients with GBM who have favorable features eventually experience recurrence and become refractory to treatment.3 Clinical trials play a significant role in the overall management of patients with GBM and, compared with patients with other cancers, a significantly higher number of patients with GBM enroll in clinical trials over the course of their disease.4

Because of the highly infiltrative nature of this disease, complete surgical resection is never fully achieved even when “gross total resection” is confirmed by MRI. Further, because of the infiltrative nature of the tumor, radiation therapy is limited in its ability to adequately target the infiltrative disease. Finally, despite the battery of available chemotherapeutic agents, options for patients with GBM are restricted by the inability of most of these agents to cross the blood-brain barrier. Because the current standard-of-care modalities have significant limitations, there has been a great interest in pursuing immunotherapeutic strategies for GBM.

CRACKING THE CODE FOR IMMUNOTHERAPY

In the past decade, many immunotherapeutic strategies such as peptide vaccines, monoclonal antibodies, cell-based vaccines, and the use of oncolytic viruses have been investigated both in the preclinical and clinical settings for patients with GBM. However, most resulted in negative clinical trial results.5,6 Checkpoint inhibitors, such as monoclonal antibodies against PD-1, are a highly effective form of immunotherapy for many solid cancers6,11; however, when tested in the phase 3 CheckMate 143 trial (NCT02017717) for patients with recurrent GBM, investigators observed no OS benefit.7,12 An observation that has emerged from the failed trials is that GBM tumors are highly heterogeneous and immunosuppressive in nature, and they actively manipulate the tumor immune microenvironment as well as the systemic immune system of the patient.13 Additionally, there is a significant interpatient variability in the robustness of the antitumor immune response mounted against the tumor that...
separates responders from nonresponders in most immunotherapy clinical trials. PD-1 is a regulatory checkpoint molecule expressed by cytotoxic effector T cells; these cells are critical for mounting successful antitumor immune response. When PD-1 binds to its ligand, PD-L1, which is expressed by cancer cells and other immune cells, the interaction renders cytotoxic T cells ineffective or exhausted. GBM is characterized by severe T-cell dysfunction.13 Monoclonal antibodies against PD-1 disrupt this interaction and boosts antitumor immune response in the process.

Although the phase 3 CheckMate 143 trial (NCT02017717) of the PD-1 inhibitor nivolumab (Opdivo) for recurrent GBM was disappointing,7 a pilot study of neoadjuvant PD-1 blockade prior to tumor resection in patients with recurrent GBM reported intriguing results. The patients’ data showed better response to this neoadjuvant strategy compared with adjuvant PD-1 blockade.14 The findings suggest that T-cell dysfunction and immunotherapy failure in GBM is a dynamic process, with significant cross-talk between the tumor and the immune system.

We are just beginning to comprehend some of the basic mechanisms that drive the failure of immunotherapy in GBM. The Malignant Brain Tumor Laboratory, University of Wisconsin (UW) Carbone Cancer Center, led by Mahua Dey, MD, is advancing the understanding of mechanisms leading to immunotherapy failure for GBM. Under a translational research study protocol, investigators are analyzing the effector T-cell dysfunction seen in patients with GBM and are examining the immune-cell infiltration in the tumor tissue and blood samples that are collected during surgery.

This is a transitional preclinical and clinical collaboration to better understand the specific immune responses of individual patients, and to develop personalized immunotherapy options for patients with GBM. The study’s primary aim is to understand the regulatory mechanisms that influence why certain patients mount better immune responses against GBM while others do not, and the results should help pave the way to designing effective immunotherapy. The study is currently open to all patients with GBM who are undergoing surgical resection at UW Health.

**REFERENCES**


Navitoclax Shows Early Signs of Clinical Benefit in Myelofibrosis

by ANITA T. SHAFFER

**THE COMBINATION OF NAVITOCLAX and ruxolitinib (Jakafi) simultaneously inhibits 2 key mechanisms that promote myelofibrosis (MF), resulting in an improvement in symptom control and positive changes in response biomarkers in patients with high-risk disease, according to Catriona Jamieson, MD, PhD.**

The dual regimen demonstrated a reduction in spleen volume and total symptom score (TSS) while improving bone marrow fibrosis, in findings from the phase 2 REFINE study (NCT03222609) presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition held virtually in December 2020. The combination also reduced the expression of driver genes and improved cytokine markers (TABLE).1

“Improving quality of life is an important goal of therapy for patients with MF, experts say. MF, one of a group of heterogeneous myeloproliferative neoplasms (MPNs), results in a heavy constitutional burden of symptoms driven by bone marrow fibrosis and extramedullary hematopoiesis, Jamieson said.

“Ruxolitinib, a JAK1/2 inhibitor approved for patients with primary and secondary MF, is effective in improving splenomegaly and disease-related symptoms. The agent “has little impact on bone marrow fibrosis, and a number of patients are refractory or develop secondary resistance,” noted investigators, in a poster presented at the 25th European Hematology Association Annual Congress in June 2020.3

Navitoclax, a small molecule like ruxolitinib, targets members of the BCL-2 family of apoptotic receptors, including BCL-X, which may prevent fibrosis in the bone marrow. Results from preclinical studies have shown that synergistic activity of JAK2 and BCL-2/BCL-X inhibitors results in cell death for JAK2-mutated cells and can help overcome resistance to JAK2-targeted therapy.3

Jamieson described the development of MF in the context of the JAK/STAT network.

“THERAPEUTIC PRIORITIES

Improving quality of life is an important goal of therapy for patients with MF, experts say. MF, one of a group of heterogeneous myeloproliferative neoplasms (MPNs), results in a heavy constitutional burden of symptoms driven by bone marrow fibrosis and extramedullary hematopoiesis, Jamieson said.

In the MPN Landmark Survey, patients reported symptoms of a severity of 6 or greater on a 10-point scale for a range of problems including fatigue, depression, headaches, sweating, unintentional weight loss, vision changes, and blood clots. MF also takes a toll on patients’ ability to work, resulting in absenteeism and early retirement.2

**TABLE. Efficacy Findings in Navitoclax Study**

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Outcomes (no. of evaluable patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen volume reduction ≥ 35% at week 24</td>
<td>27% (9 of 34)</td>
</tr>
<tr>
<td>Total symptom score reduction ≥ 50% at week 24</td>
<td>30% (6 of 20)</td>
</tr>
<tr>
<td>Driver gene reductions &gt; 10% in JAK2 or CALR</td>
<td>46% (12 of 26)</td>
</tr>
<tr>
<td>Bone marrow fibrosis improvements of at least 1 grade at any time</td>
<td>29% (10 of 34)</td>
</tr>
<tr>
<td>Bone marrow improvement at week 24</td>
<td>21% (7 of 34)</td>
</tr>
</tbody>
</table>

Ruxolitinib, a JAK1/2 inhibitor approved for patients with primary and secondary MF, is effective in improving splenomegaly and disease-related symptoms. The agent “has little impact on bone marrow fibrosis, and a number of patients are refractory or develop secondary resistance,” noted investigators, in a poster presented at the 25th European Hematology Association Annual Congress in June 2020.3

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Jamieson described the development of MF in the context of the JAK/STAT network. “This pathway is upregulated in the majority of patients with these myeloproliferative neoplasms. In some, it’s based on a mutation in JAK2 that prevents the gene from being turned off; in others, a mutation in CALR can...
also activate JAK/STAT signaling. And in the third group, it’s through the MPL mutation, which activates signaling through the thrombopoietin receptor more readily.”

Moreover, patients with MF who harbor high molecular risk (HMR) mutations at diagnosis have worse survival outcomes and are more likely to experience leukenic transformation to more aggressive disease, Jamieson said. “There is a great unmet need for therapies that are effective in myelofibrosis, regardless of disease biology or risk,” she noted.

**CLINICAL TRIAL DETAILS**

In the ongoing REFINE study, patients include those with primary or secondary MF with splenomegaly who have had ruxolitinib failure after 12 weeks or more of continuous treatment. Participants receive navitoclax at a starting dose of 50 mg once daily along with ruxolitinib twice daily at their dose at study entry. The navitoclax dose can be increased to a maximum of 300-mg daily, provided the patient’s platelet count is greater than 100 x 10^9/L. 3

The primary end point is the percentage of patients who achieve a spleen volume reduction (SVR) of 35% or greater from baseline through week 24. Secondary end points are the percentage of participants reaching a reduction in TSS of 50% or greater, platelet response, and change in grade of bone marrow fibrosis.

Overall, Jamieson said, the primary objectives of the study are to evaluate whether the presence of HMR mutations or the total number of mutated genes has an impact on clinical outcomes and to discover how the combination therapy affects inflammatory cytokines. Investigators are performing mutational analyses at baseline and week 24, including next-generation sequencing with a 54-gene assay of variant allele frequency (VAF) in peripheral blood samples. Cytokine mutational analyses at baseline and week 24, anemia response, and change in grade of bone marrow fibrosis.

**EFFICACY OUTCOMES**

At the ASH meeting, investigators reported data for 34 patients with MF who had received at least 1 dose of navitoclax plus ruxolitinib as of February 28, 2020. The median age of participants was 68 years (range, 42-86), ECOG performance status was 0 or 1, and median duration of prior ruxolitinib therapy was 20 months (range, 4-97). The median spleen volume was 1695 cm^3 (range, 465-5047). 1

In terms of mutations, 79% of participants had a JAK2 mutation and 21% had a CALR alteration. In all, 58% of patients (n = 19) had mutations in HMR genes, most frequently in ASXL1, followed by SRSF2, EZH2, U2AF1, and IDH1. Of those with HMR gene mutations, 42% (n = 8) had 2 or more aberrations (FIGURE). 1

At week 24, the combination therapy resulted in an SVR reduction of 27% in 34 evaluable patients; a TSS reduction in 30% of 20 participants; and a VAF reduction of 10% or more in the driver genes of JAK2 or CALR in 46% of 26 patients. The therapy also led to bone marrow fibrosis improvements of at least 1 grade at any time in 29% of 34 patients.

Investigators observed treatment-emergent adverse events (TEAEs) in all patients, most commonly thrombocytopenia (88%), diarrhea (68%), and fatigue (62%). They reported TEAEs of grade 3 or greater severity in 85% of patients, most frequently thrombocytopenia (53%), anemia (32%), and pneumonia (12%). “Thrombocytopenia is manageable with dose modification and the pneumonia will require a little bit more investigation,” Jamieson said.

“We’re very excited about the results of this study in terms of reducing the variable allele frequency as well as bone marrow fibrosis grade,” Jamieson said. “The efficacy may be borne out over time.”

The impact on bone marrow fibrosis was not affected by the presence of total mutations or HMR alterations. At week 24, 4 of 5 patients who reached a molecular response, defined as a reduction of 20% or greater in driver genes, demonstrated evidence of fibrosis reversal of at least 1 grade. “This is a really important finding from this study,” she said.

Additionally, investigators found a correlation between changes in spleen volume and MF-associated cytokine levels measured from baseline. Levels of 4 cytokines associated with TSS improvement were more moderate for beta-2 microglobulin, tumor necrosis factor receptor 2, tissue inhibitor of metallopeptases 1, and vascular cell adhesion molecule 1. “It was fairly striking at week 12 and week 24,” Jamieson said. “That may be the pivotal part of this trial—defining new biomarkers of response in addition to showing nice efficacy.”

Overall, Jamieson said, the research advances understanding of MF. “This is a high-risk group of patients that desperately needs newer therapies and I think this team has gotten it right in terms of not just the combination strategy of BCL-X inhibition in addition to JAK2 inhibition but also in terms of trying to predict who’s likely to respond.”

In July 2020, AbbVie, the company developing navitoclax, opened the randomized phase 3 TRANSFORM-1 trial (NCT04472598) in patients with primary or secondary MF who have not been previously treated with a JAK2 inhibitor. The trial, which aims to recruit 230 participants, will compare the combination of navitoclax plus ruxolitinib with placebo plus ruxolitinib. The primary end point is an SVR of 35% or greater at week 24. 4
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage including subdural hematoma, gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®. The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. In IMBRUVICA® clinical trials, 3.1% of patients taking IMBRUVICA® without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.
LEADING THE WAY WITH
A WAVE OF EVIDENCE

IMBRUVICA® is the only BTKi with 10 approvals, across 6 indications, based on 10 pivotal trials

INDICATIONS

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- CLL/SLL with 17p deletion
- Waldenström’s macroglobulinemia (WM)
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
- Mantle cell lymphoma (MCL) who have received at least one prior therapy*
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy*

*Accelerated approval was granted for the MCL and MZL indications based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

BTKi=Bruton’s tyrosine kinase inhibitor.

Confidence built on 150,000+ patients treated worldwide

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. 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. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%), diarrhea (41%), anemia (38%), neutropenia (35%), musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%), thrombocytopenia (16%), and pneumonia (14%).

Approximately 7% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (38%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

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

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤7 days). See dose modification guidelines in USPI sections 2.4 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please see brief summary on the following pages.

2. Data on file, REF-13821. Pharmacyclics LLC.

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IMBRUVICA®

(ibrutinib)

560, 420, 280, 140 mg tablets | 140 mg capsules
Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE
Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial [see Clinical Studies (14.1) in Full Prescribing Information].

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

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

Waldenström’s Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström’s macroglobulinemia (WM).

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. Accelerated approval was granted for this indication based on overall response rate [see Clinical Studies (14.4) in Full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestional bleeding, hematura, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,638 patients exposed to IMBRUVICA in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA. The mechanism for the bleeding events is not well understood.

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

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA in clinical trials [see Adverse Reactions]. Cases of progression of multisystemic fungal infections have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA. Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachycardias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Dosage and Administration (2.3) in Full Prescribing Information].

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

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

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (8%).

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. 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 [see Use in Specific Populations].

ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

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

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

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

The most common Grade 3 or 4 treatment-related adverse reactions were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. 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 [see Use in Specific Populations].

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14</td>
<td>8*</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

*Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. 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 [see Use in Specific Populations].

IMBRUVICA® (ibrutinib) tablets, for oral use
IMBRUVICA® (ibrutinib)

Study 1102: Adverse reactions and laboratory abnormalities from the treatment due to adverse reactions. These included pneumonia, hemorrhage, and cough.

The most commonly occurring adverse reactions in patients with CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.8 months are presented in Tables 3 and 4.

### Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>27</td>
<td>5†</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements and adverse reactions

† Includes one event with a fatal outcome.

### Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients in Study 1102

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

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

### Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>69</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>53</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>49</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td>Second malignancies</td>
<td>10</td>
<td>2†</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

### Table 6: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>69</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>53</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and four randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS, and iLLUMINATE) in patients with CLL/SLL (n=1,506 total and n=781 patients exposed to IMBRUVICA). Patients with creatinine clearance (CrCl) < 30 mL/min, AST or ALT ≥ 2.5 x ULN (upper limit of normal), or total bilirubin ≥ 1.5 x ULN (unless of non-hepatic origin) were excluded from these trials. Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 386 randomized patients with treatment naïve CLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil in combination with obinutuzumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, HELIOS included 574 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil, HELIOS included 574 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab, and iLLUMINATE included 228 randomized patients with treatment naïve CLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab.

The most commonly occurring adverse reactions in patients with CLL/SLL receiving IMBRUVICA (> 20%) were neuropathy, thrombocytopenia, anemia, diarrhea, rash, musculoskeletal pain, bruising, nausea, fatigue, pyrexia, hemorrhage, and cough.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia. Adverse reactions leading to dose reduction occurred in approximately 7% of patients.

### Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.8 months are presented in Tables 3 and 4.

1. One patient death due to histiocytic sarcoma.
Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 1</td>
<td>11 2</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>15 12</td>
<td>13 10</td>
</tr>
<tr>
<td>Sinusitis*</td>
<td>11 1</td>
<td>6 0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 4</td>
<td>5 1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>24 3</td>
<td>13 0</td>
</tr>
<tr>
<td>Petechiae</td>
<td>14 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Bruising*</td>
<td>12 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>28 2</td>
<td>18 1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17 1</td>
<td>7 0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19 0</td>
<td>23 1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 2</td>
<td>10 1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14 1</td>
<td>6 0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 0</td>
<td>5 0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>11 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>10 0</td>
<td>3 0</td>
</tr>
</tbody>
</table>

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

* Includes multiple ADR terms

† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36 0</td>
<td>39 1</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>51 23</td>
<td>57 26</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>52 5</td>
<td>45 10</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36 0</td>
<td>21 0</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 8% in the ofatumumab arm) occurred in patients.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 4</td>
<td>17 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 1</td>
<td>39 1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 1</td>
<td>16 0</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>14 1</td>
<td>4 1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 0</td>
<td>20 1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 3</td>
<td>11 1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11 0</td>
<td>2 0</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36 0</td>
<td>39 2</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>55 28</td>
<td>67 31</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>47 7</td>
<td>58 14</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (1% in the IMBRUVICA arm vs 3% in the chlorambucil arm) and neutropenia (11% in the IMBRUVICA arm vs 12% in the chlorambucil arm) occurred in patients.

HELIOS: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.∗ Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm.
Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.∗ Includes multiple ADR terms
† Includes one event with a fatal outcome.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.∗ Includes multiple ADR terms
† Includes one event with a fatal outcome.

**Table 9: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS**

**Table 10: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)**
**IMBRUVICA® (ibrutinib)**

### Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising*</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rash*</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage*</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypertension*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Fatigue</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spams</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin infection*</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

### Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

<table>
<thead>
<tr>
<th>Percent of Patients (N=94)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>21</td>
<td>6</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (4%) and neutropenia (7%) occurred in patients.

**INNOVATE:** Adverse reactions described below in Table 13 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naive or previously treated WM in INNOVATE.

### Table 13: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE (continued)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + R (N=75)</th>
<th>Placebo + R (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Fatigue</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>17</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising*</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Rash*</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>14</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Muscle spams</td>
<td>19</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>11</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

† Includes one event with a fatal outcome.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

**Study 1121:** Adverse reactions and laboratory abnormalities described below in Tables 14 and 15 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

### Table 14: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising*</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rash*</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage*</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypertension*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Fatigue</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spams</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin infection*</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sinusitis*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

† Includes one event with a fatal outcome.
and Table 17 reflect exposure to IMBRUVICA with a median duration of 4.4 months in patients receiving IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

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

Additional Important Adverse Reactions: Cardiac Arrhythmias: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 9% versus 1.4% and 4% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively.

Treatment-emergent Grade 4 neutropenia occurred in 2% of patients.

The body system and individual ADR preferred terms are sorted in descending frequency order.

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

### Table 14: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Hyperalbunemia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>30</td>
<td>2†</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lough</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 15: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

### Table 16: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

The system organ class and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.
† Includes 2 events with a fatal outcome.

### Table 17: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>24</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 18: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Head peripheral</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising*</td>
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<td>Injury, poisoning and procedural complications</td>
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<td>Fall</td>
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</table>
IMBRUVICA® (ibrutinib)

- Hepatobiliary disorders: hepatotoxicity including acute and/or chronic hepatitis, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutritional disorders: tumor lysis syndrome [see Warnings & Precautions]
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), erythroderma, panniculitis
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA are recommended when used concomitantly with cisapride, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, stavudine, tizanidine, trovafloxacin, voriconazole, and moderate CYP3A inhibitors [see Dosage and Administration (2.4) in Full Prescribing Information]. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.4) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities (see Data). If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day, ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily. Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: Pregnancy Testing: Conduct pregnancy testing in females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception: Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

IMBRUVICA® (ibrutinib)

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

Hematologic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria. Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].

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

PATIENT COUNSELING INFORMATION

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

- Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].
- Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].
- Cardiac Arrhythmias: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions].
- Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].
- Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].
- Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].
- Embryo-fetal toxicity: Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA [see Warnings and Precautions].
- Inform patients to take IMBRUVICA orally once daily according to their physician’s instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.6) in Full Prescribing Information].
- Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

Active ingredient made in China.

Distributed and Marketed by: Pharmacyclics LLC
Sunnyvale, CA USA 94085

and

Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent http://www.imbruvica.com

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PRC-06112
A New Crop of ER-Targeting Agents Takes Root

by JANE DE LARTIGUE, PhD

ALTHOUGH ENDOCRINE THERAPIES have revolutionized the treatment of breast cancers driven by the estrogen receptor (ER), the development of resistance remains a major challenge that limits long-term remission with currently available drugs. Now there is a growing trend toward developing more potent endocrine therapies with the potential to address this challenge.

Data highlighted at conferences in the last year showcased the significant potential of oral selective ER downregulators (SERDs) being developed for heavily pretreated ER-positive breast cancers, including those that harbor ESR1 mutations, a common mechanism of resistance.

Treatment frontrunners include Sanofi’s amcenestran (SAR439859), Genentech’s giredestrant (GDC-9545), and AstraZeneca’s AZD9833, with all 3 companies betting on their drug’s success in recently initiated phase 3 clinical trials. Meanwhile, other pharmaceutical companies are investing in new drug designs, such as Connecticut-based Arvinas’ first-in-class proteolysis-targeting chimera (PROTAC)-based drug, ARV-471 (TABLE).

STANDARD OF CARE

Nearly 80% of breast cancers express the ER, making it the most significant driver of this tumor type. In patients with ER-positive breast cancer, endocrine therapy has been the gold standard for decades, beginning with the approval of tamoxifen in the 1970s. Tamoxifen is a selective ER modulator (SERM), a class of agents that act as either ER agonists or antagonists, depending on the tissue. Tamoxifen competes with estrogen for binding to the ER and blocks estrogen-dependent gene transcription and the resulting cellular outcomes.1

Tamoxifen remains a recommended treatment option for patients with ER-positive breast cancer and has been joined by the FDA-approved SERMs toremifene (Fareston) and raloxifene (Evista).2,3 These drugs are often mistakenly referred to as antiestrogens; however, their mechanism of action is much more complex. They can elicit a spectrum of effects, from mimicking estrogen to almost purely antiestrogenic activity.4,5

The mechanisms behind these processes are thought to be related to the SERMs’ interfering with the ER’s ability to recruit coregulatory proteins upon activation. The balance between the activating and repressive coregulatory proteins present within a specific cell may therefore dictate the outcome of SERM activity.4,5

Regardless of the underlying biology, these varying events have important implications. Because of tamoxifen’s estrogenic activity in certain tissues, serious adverse effects (AEs) are associated with the drug’s long-term use.5,6

A number of other endocrine therapies have been developed over the years. SERDs antagonize ER activity in a manner similar to that of SERMs, but they have a much higher binding affinity and also induce ER degradation. SERDs are purely antiestrogenic, with none of the agonist effects of SERMs. Currently, fulvestrant (Faslodex) is the only FDA-approved SERD in the breast cancer setting.5,6

Members of a third class of endocrine therapy, aromatase inhibitors (AIs), act indirectly on the ER signaling pathway by inhibiting the activity of the aromatase enzyme involved in the biosynthesis of estrogens from androgens. AIs, which include the steroidal compound exemestane and the nonsteroidal drugs letrozole and anastrozole are recommended treatment options in the adjuvant setting, either as initial adjuvant therapy or following tamoxifen. In the metastatic setting, they are the recommended first-line treatment, demonstrating advantages over tamoxifen.5,7

THE CHALLENGE OF RESISTANCE

The benefits of endocrine therapy in ER-positive breast cancer are irrefutable. However, many patients either will have intrinsic resistance or will develop resistance over the course of treatment, which is a major barrier to long-term remission.

A greater understanding of the mechanisms underlying resistance to endocrine therapy has translated into new treatment options designed to tackle resistance. Exploiting cross talk between ER signaling and other intracellular signaling pathways, inhibitors of cyclin-dependent kinases (CDKs) 4/6 and PI3K are now approved by the FDA for the treatment of patients with ER-positive breast cancer.7 These drugs are currently approved for use in combination with endocrine therapy (although abemaciclib [Verzenio] also has a monotherapy indication) in the advanced or metastatic setting. Ongoing clinical trials are looking at such combinations in early-stage breast cancer.

Activating mutations in the ESR1 gene, which encodes the main form of ER in the breast, represent another significant mechanism of resistance to currently available endocrine therapies. De novo ESR1 mutations are found at low frequencies in patients with newly diagnosed disease, but acquired mutations occur in up to 40% of patients who have previously received endocrine therapy.8,9 Most common are the Y537S and D538G point mutations, accounting for 14% and 36% of somatic ESR1 mutations, respectively.10

Although ESR1 mutations promote some level of resistance to all currently available endocrine therapies, fulvestrant appears to be the least affected.11,12 However, its potency...
is believed to be limited by its intramuscular route of administration, and an oral SERD could prove more effective and less susceptible to endocrine resistance.13

**ORAL SERDS HIT THEIR STRIDE**

Initial efforts to develop orally bioavailable fulvestrant-like steroidal SERDs were unsuccessful.13 A growing number of nonsteroidal oral SERDs are in clinical development and have demonstrated promising antitumor activity in patients with advanced ER-positive breast cancer, including those with ESR1 mutations.

**Amcenestrant**

Sanofi is developing amcenestrant, which has shown early signs of clinical efficacy in the phase 1/2 AMEERA-1 trial (NCT03284957) in postmenopausal women with heavily pretreated ER-positive, HER2-negative advanced or metastatic breast cancer. AMEERA-1 is evaluating amcenestrant as monotherapy and in combination with other anticancer therapies.14

Updated results from the monotherapy cohorts were reported at the 2020 San Antonio Breast Cancer Symposium (SABCS). Pooled data from 62 women included results from those who had received escalating doses from 150 mg to 600 mg once daily in part A (n = 13) and 400 mg once daily during dose expansion (part B; n = 49). All patients

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**The Network**

**ER Signaling as a Breast Cancer Driver**

**THE ESTROGEN RECEPTOR (ER)** is responsible for most of the cellular effects of the estrogen hormones (estrone, estradiol, and estriol), which play a central role in female mammary and reproductive development. The ER does this predominantly through its ability, unique to the nuclear receptor superfamily to which it belongs, to act as a transcription factor as well as a receptor, orchestrating an extraordinarily complex signaling pathway.1-3

The ESR1 and ESR2 genes encode 2 forms of the receptor, ERα and ERβ, respectively; the former is dominant in the breast and is the main driver of breast cancer. Both isoforms are composed of multiple domains, including DNA-binding domains (DBDs), ligand-binding domains (LBDs), and N-terminal domains (NTDs).1-3

The LBD is composed of 12 helices and contains 1 of 2 activation function (AF) domains, AF-2, which facilitates activation of the ER; the other, AF-1 is found in the NTD. Upon ligand binding, which is mediated by the AF-2 domain, the ER is activated and translocates to the nucleus to function as a transcription factor. However, ER can respond to a large variety of other intracellular and extracellular signals in a ligand-independent manner; this activity is mediated by the AF-1 domain.1,3

In the absence of ligand, the ER is found in a complex with chaperone proteins such as HSP90, which keeps it in an inactive state. ER also is constantly degraded by the ubiquitin-proteasome system, which further keeps its activity in check.4

In the “classical” ER signaling pathway, estrogen binding induces a conformational change in the receptor, which then dissociates from its chaperones and forms homodimers. Helix 12 of the LBD folds over and seals the ligand-binding pocket while exposing the AF-2 domain. This domain acts as a platform for interaction with a variety of coregulatory proteins that fine-tune ER activity by recruiting other proteins, such as histone-modifying enzymes.1-3,5

In the nucleus, the resulting multiprotein complex binds, through the ER’s DBD, to specific sites in the promoters of target genes known as estrogen response elements. Depending on the specific proteins contained within the ER complex, this binding results in the transcriptional enhancement or repression of a plethora of genes, including those involved in cell proliferation and survival, with a variety of functional outcomes depending on the cellular context (FIGURE).1,3

Prolonged exposure to estrogen is linked to an increased risk of breast cancer development,4 and ligand-induced ER signaling is strongly implicated in the development of a majority of breast cancers. Additionally, ligand-independent signaling has been found to play an important role in resistance to endocrine therapy.7,8

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For a full list of references, see the article at OncLive.com.
had received prior endocrine therapy in the advanced setting, with approximately half having received 3 or more lines. Among the 59 evaluable patients, the objective response rate (ORR)—all partial responses (PRs)—was 8.5%, and the clinical benefit rate (CBR) was 33.9%. Patients with (n = 30) and without (n = 28) ESR1 mutations derived similar clinical benefit from amcenestrant (CBR, 36.7% vs 32.1%, respectively).

Of note, the ORR and CBR were higher in a subset of patients who had not received prior therapy with CDK4/6 inhibitors, mTOR inhibitors, or fulvestrant compared with the

### TABLE. ER-Targeting Therapies in Development for ER-positive, HER2-negative Breast Cancer

<table>
<thead>
<tr>
<th>Agent (developer)</th>
<th>Ongoing trial(s)</th>
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<td>+ Palbociclib vs anastrozole + palbociclib</td>
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<td>Rintodestrant (G1T48; G1 Therapeutics)</td>
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<td><strong>SERMs</strong></td>
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</table>

ER, estrogen receptor; DCIS, ductal carcinoma in situ; LHRH, luteinizing hormone-releasing hormone; SERD, selective estrogen receptor downregulator; SERM, selective estrogen receptor modulator; SOC, standard of care.

*Trial is currently active but not recruiting patients.
ORGOVYX achieved sustained testosterone suppression

- 97% of men achieved and maintained testosterone suppression to <50 ng/dL from Day 29 through Week 48 with ORGOVYX.

### MAJOR EFFICACY OUTCOME MEASURE: SUSTAINED TESTOSTERONE SUPPRESSION RATE (TESTOSTERONE LEVELS <50 ng/dL FROM DAY 29 THROUGH WEEK 48)

![Graph showing sustained testosterone suppression rates]

**Results from the HERO study, a multinational, randomized, open-label, phase 3 trial in 934 men with advanced prostate cancer. Patients were randomized 2:1 to receive ORGOVYX (360 mg on the first day followed by daily doses of 120 mg orally [n=624]) or leuprolide acetate (22.5 mg injection [or 11.25 mg] in Japan and Taiwan per local guidelines] subcutaneously every 3 months [n=310]) for 48 weeks.**

CI=confidence interval.
1 Kaplan-Meier estimates within each group.
2 The testosterone suppression rate of the subgroup of patients receiving 22.5 mg leuprolide (n=113) was 88.0% (95% CI: 83.4%, 91.4%).
3 Two patients in each arm did not receive the study treatment and were not included.

### INDICATION

ORGOVYX is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the treatment of adult patients with advanced prostate cancer.

### IMPORTANT SAFETY INFORMATION

**Warnings and Precautions**

**QT/QTc Interval Prolongation:** Androgen deprivation therapy, such as ORGOVYX may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

**Embryo-Fetal Toxicity:** The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

**Laboratory Testing:** Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

**Adverse Reactions**

**Serious adverse reactions** occurred in 12% of patients receiving ORGOVYX. Serious adverse reactions in ≥0.5% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ORGOVYX including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX.

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Introducing ORGOVYX, the only once-a-day* oral androgen deprivation therapy for advanced prostate cancer1,2

*One pill, once a day, after initial loading dose of 3 pills.

ORGOVYX offers a new option for testosterone control1-3

- **RAPID TESTOSTERONE SUPPRESSION WITHOUT A SURGE:** 56% of men treated with ORGOVYX achieved testosterone suppression to <50 ng/dL on Day 4
  - 0% of men treated with leuprolide had testosterone levels <50 ng/dL on Day 4
- **PROFOUND TESTOSTERONE SUPPRESSION:** 95% of men treated with ORGOVYX achieved profound testosterone suppression to <20 ng/dL on Day 29
  - 57% of men treated with leuprolide had testosterone levels <20 ng/dL on Day 29
- **90-DAY TESTOSTERONE RECOVERY:** in a substudy, 55% of the 137 men treated with ORGOVYX had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after treatment discontinuation
  - 3% of 47 men treated with leuprolide had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after discontinuation

*Kaplan-Meier estimates within each group.
*This endpoint was analyzed for exploratory purposes without formal testing. The data from the leuprolide arm were not included in the US Prescribing Information for ORGOVYX.

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

Most common adverse reactions (≥10%) and laboratory abnormalities (≥15%) in patients receiving ORGOVYX were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (27%), fatigue (26%), aspartate aminotransferase increased (18%), constipation (12%), and diarrhea (12%).

**Drug Interactions**

**Co-administration of ORGOVYX with a P-gp inhibitor** increases the area under the curve (AUC) and maximum concentration (Cmax) of ORGOVYX, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors. If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions. Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors. If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

**Co-administration of ORGOVYX with a combined P-gp and strong CYP3A inducer** decreases the AUC and Cmax of ORGOVYX, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers. If co-administration is unavoidable, increase the ORGOVYX dose to 240 mg once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended ORGOVYX dose of 120 mg once daily.

Please see Brief Summary of Prescribing Information for ORGOVYX on adjacent pages.

**References:**

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1 INDICATIONS AND USAGE

ORGOVYX is indicated for the treatment of adult patients with advanced prostate cancer.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QT/QTc Interval Prolongation

Androgen deprivation therapy, such as ORGOVYX may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

5.2 Embryo-Fetal Toxicity

The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during the period of organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on area under the curve (AUC). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

5.3 Laboratory Testing

Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropin and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

6 ADVERSE REACTIONS

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

- QT/QTc Interval Prolongation.

6.1 Clinical Trials Experience

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

The safety of ORGOVYX was evaluated in HERO, a randomized (2:1), open-label, clinical study in patients with advanced prostate cancer. Patients received orally administered ORGOVYX as a loading dose of 360 mg on the first day followed by 120 mg taken orally once daily (n = 622) or received leuprolide acetate 11.25 mg is a dosage regimen that is not recommended for this indication in the US. Among patients who received ORGOVYX, 91% were exposed for at least 48 weeks. Ninety-nine (16%) patients received concomitant radiotherapy and 17% (33) patients received concomitant enzalutamide with ORGOVYX.

Serious adverse reactions occurred in 12% of patients receiving ORGOVYX. Serious adverse reactions in ≥ 5.0% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ORGOVYX including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX.

Permanent discontinuation of ORGOVYX due to an adverse reaction occurred in 3.5% of patients. Adverse reactions which resulted in permanent discontinuation of ORGOVYX in ≥ 0.3% of patients included atrioventricular block (0.3%), cardiac failure (0.3%), hemorrhage (0.3%), increased transaminases (0.3%), abdominal pain (0.3%), and pneumonia (0.3%).

Dosage interruptions of ORGOVYX due to an adverse reaction occurred in 2.7% of patients. Adverse reactions which required dosage interruption in ≥ 0.3% of patients included fracture (0.3%).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ORGOVYX

P-gp Inhibitors

Co-administration of ORGOVYX with a P-gp inhibitor increases the AUC and the maximum concentration (Cmax) of relugolix, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors.

If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions.

Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors.

If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

Combined P-gp and Strong CYP3A Inducers

Co-administration of ORGOVYX with a combined P-gp and a strong CYP3A inducer decreases the AUC and Cmax of relugolix, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers.

If co-administration is unavoidable, increase the ORGOVYX dose. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended dose of ORGOVYX once daily.

The most common adverse reactions (≥ 10%) and laboratory abnormalities (≥ 15%), were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (ALT) (27%), fatigue (26%), aspartate aminotransferase increased (AST) (18%), constipation (12%), and diarrhea (12%).

Table 1 summarizes the adverse reactions in HERO.

Table 1: Adverse Reactions (≥ 10%) of Patients with Advanced Prostate Cancer Who Received ORGOVYX in HERO

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ORGOVYX N = 622</th>
<th>Leuprolide Acetate N = 308</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>54</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>30</td>
<td>1.1</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>26</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

a Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, myalgia, bone pain, neck pain, arthritis, musculoskeletal stiffness, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, and musculoskeletal discomfort.

Clinically relevant adverse reactions in < 10% of patients who received ORGOVYX included increased weight, insomnia, gynecomastia, hyperhidrosis, depression, and decreased libido.

Table 2 summarizes the laboratory abnormalities in HERO.

Table 2: Select Laboratory Abnormalities (≥ 15%) That Worsened from Baseline in Patients with Advanced Prostate Cancer Who Received ORGOVYX in HERO

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>ORGOVYX*</th>
<th>Leuprolide Acetate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>44</td>
<td>2.9</td>
</tr>
<tr>
<td>Triglycerides increased</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>ALT increased</td>
<td>27</td>
<td>0.3</td>
</tr>
<tr>
<td>AST increased</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>28</td>
<td>0.5</td>
</tr>
</tbody>
</table>

a The denominator used to calculate the rate varied from 611 to 619 in the ORGOVYX arm and from 301 to 306 in the leuprolide arm based on the number of patients with a baseline value and at least one post-treatment value.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The safety and efficacy of ORGOVYX have not been established in females.

Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. There are no human data on the use of ORGOVYX in pregnant females to inform the drug-associated risk. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC (see Data). Advise patients of the potential risk to the fetus.

Data
Animal Data
In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC).

8.2 Lactation

Risk Summary
The safety and efficacy of ORGOVYX at the recommended dose of 120 mg daily have not been established in females. There are no data on the presence of relugolix in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix and/or its metabolites were present in milk of lactating rats (see Data).

Data
Animal Data
In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Contraception
Males
Based on findings in animals and mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

Infertility
Males
Based on findings in animals and mechanism of action, ORGOVYX may impair fertility in males of reproductive potential.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 622 patients who received ORGOVYX in the HERO study, 81% were 65 years of age or older, while 35% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. There was no clinically relevant impact of age on the pharmacokinetics of ORGOVYX or testosterone response based on population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses in men 45 to 91 years of age.

12.3 Pharmacokinetics

Specific Populations
No clinically meaningful differences in the pharmacokinetics of relugolix were observed based on age (45 to 91 years), race/ethnicity (Asian [19%), White [71%], Black/African American [8%]), body weight (41 to 193 kg), mild to severe renal impairment (creatinine clearance [ClCr] 15 to 89 mL/min, as estimated by the Cockcroft-Gault equation), or mild to moderate hepatic impairment (Child-Pugh A or B). The effect of end-stage renal disease with or without hemodialysis or severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of relugolix has not been evaluated.

Drug Interactions Studies
Clinical Studies
Combined P-gp and Moderate CYP3A Inhibitor: Co-administration with erythromycin (P-gp and moderate CYP3A3 inhibitor) increased the AUC and Cmax of relugolix by 6.2-fold.

Combined P-gp and Strong CYP3A Inducer: Co-administration with rifampin (P-gp and strong CYP3A3 inducer) decreased the AUC and Cmax of relugolix by 55% and 23%, respectively.

Other Drugs: No clinically significant differences in the pharmacokinetics of relugolix were observed when co-administered with voriconazole (strong CYP3A inhibitor), atorvastatin, ezetimibe, or acid-reducing agents. No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) or rosuvastatin (BCRP substrate) were observed upon co-administration with relugolix.

In Vitro Studies
Cytochrome P450 (CYP) Enzymes: Relugolix is a substrate of CYP3A and CYP2C8. Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Relugolix is an inducer of CYP3A and CYP2B6, but not an inducer of CYP1A2.

Transporter Systems: Relugolix is a substrate of P-gp, but not a substrate of BCRP. Relugolix is an inhibitor of BCRP and P-gp, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 75 or 224 times, respectively, the human exposure at the recommended dose of 120 mg daily based on AUC.

Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

In humans GnRH-receptor knock-in male mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses ≥ 3 mg/kg twice daily for 28 days. The effects of relugolix were reversible, except for testes weight, which did not fully recover within 28 days after drug withdrawal. In a 39-week repeat-dose toxicity study in monkeys, there were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at the recommended dose of 120 mg daily based on AUC).

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, gastrointestinal tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses ≥ 100 mg/kg (approximately 18 times the human exposure at the recommended dose based on AUC). In a monkey 39-week toxicity study, this effect was observed at doses ≥ 1.5 mg/kg (approximately 0.6 times the human exposure at the recommended dose based on AUC) and demonstrated evidence of reversibility after cessation of treatment. The significance of this finding in humans is unknown.

17 PATIENT COUNSELING INFORMATION

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

OT/QTc Interval Prolongation

• Advise patients that androgen deprivation therapy treatment with ORGOVYX may prolong the QT interval. Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately for signs or symptoms of QT prolongation.

Androgen Deprivation

• Inform patients about adverse reactions related to androgen deprivation therapy with ORGOVYX, including hot flashes, flushing of the skin, increased weight, decreased sex drive, and difficulties with erectile function.

Embryo-Fetal Toxicity

• Inform patients that ORGOVYX can be harmful to a developing fetus and can cause loss of pregnancy.

• Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

Infertility

• Inform patients that ORGOVYX may cause infertility.

Manufactured by Bushu Pharmaceuticals, Ltd, Kawasaki, Saitama, Japan
Manufactured for Myovant Sciences, Inc., Brisbane, CA 94005
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overall cohort of patients who generally had been heavily pretreated (ORR, 21.4% vs 8.5%; CBR, 64.3% vs 33.9%). These findings support the development of amencanestrant as first-line therapy, which is being evaluated in the AMEERA-5 trial (NCT04478266).

Amencanestrant displayed a favorable safety profile, with exclusively grade 1 or 2 treatment-related adverse effects (TRAEs), most commonly hot flush, constipation, arthralgia, decreased appetite, vomiting, diarrhea, nausea, and fatigue. No patients discontinued therapy due to AEs.14

**Giredestrant**

Initial data from a first-in-human phase 1 trial (NCT03332797) of another oral SERD, giredestrant, were presented at SABCS in 2019. They showed encouraging activity in patients with previously treated advanced breast cancer, including those with ESR1-mutant tumors.15 The recommended phase 2 dose identified in this dose-escalation portion of the trial, 100 mg once daily, was then explored in a dose-expansion phase as monotherapy and in combination with palbociclib (Ibrance) in postmenopausal women. Pre- and perimenopausal patients also received a luteinizing hormone-releasing hormone agonist.

Results from the dose-expansion phase were presented at the 2020 American Society of Clinical Oncology meeting. Eighty-eight patients had been enrolled in 2 cohorts (cohort A, giredestrant monotherapy, n = 40; and cohort B, giredestrant plus palbociclib, n = 48).

The 40 evaluable patients in cohort A had a median progression-free survival (PFS) of 7.8 months (95% CI, 5.3-11.4) and an ORR of 13% (95% CI, 4%-30%).

Giredestrant monotherapy was well tolerated, with mostly grade 1 or 2 TRAEs and no discontinuations. In cohort B, giredestrant demonstrated a median PFS of 9.3 months (95% CI, 8.9-not evaluable) and an ORR of 33% (95% CI, 20%-49%) among 43 evaluable patients.

Most AEs also were of grade 1 or 2 severity in the combination arm, with 1 serious AE of grade 3 QT prolongation in a patient with preexisting coronary artery disease.16

The phase 3 preservERA Breast Cancer trial of giredestrant in combination with palbociclib in patients with metastatic breast cancer is ongoing (NCT04546009).

**AZD9833**

AstraZeneca’s AZD9833 has also advanced into phase 3 clinical testing. In the phase 1 SERENA-1 trial (NCT03616587), as of August 2020, a total of 146 patients had received AZD9833 either as monotherapy (n = 98) across dose-escalation and expansion cohorts (parts A and B, respectively) or in combination with palbociclib (n = 48; parts C and D).

The median number of prior lines of therapy was 3 for patients in the monotherapy parts and 2 for those treated with combination therapy. The ORR and CBR for monotherapy were 10.0% and 35.3%, respectively, and median PFS was 5.4 months. In CDK inhibitor-naïve patients treated with combination therapy, the ORR and CBR were 14.3% and 71.4%, respectively.

The majority of TRAEs were of grade 1 or 2 severity and most commonly included anemia, fatigue, lymphopenia, nausea, neutropenia, thrombocytopenia, and reduced white blood cell count. The 5 dose-limiting toxicities (3 for monotherapy and 2 for combination therapy) were managed with dose interruption or reduction. There were 2 serious AEs potentially related to AZD9833 in the monotherapy arm. No patients discontinued treatment due to TRAEs.17

A number of clinical trials testing AZD9833 are ongoing, including the phase 3 SERENA-4 trial. In this study, investigators are evaluating the combination of AZD9833 and palbociclib in patients with treatment-naïve advanced or metastatic breast cancer (NCT04711252).

**Elacestrant**

Other notable SERDs in development include elacestrant (RAD-1901). Findings from a phase 1 study (NCT02338349) showed that elacestrant monotherapy resulted in an ORR of 19.4% among 31 heavily pretreated patients who received the recommended phase 2 dose of 400 mg once daily. No dose-limiting toxicities occurred and the most common AEs were nausea, increased blood triglycerides, and decreased blood phosphorus.18

In September 2020, Radius Health reported that the ongoing phase 3 EMERALD trial (NCT03778931), comparing elacestrant against standard endocrine therapy in patients with previously treated advanced breast cancer, had reached its enrollment goal of 466 patients, including 220 with ESR1 mutations.19

**ADDITIONAL NOVEL STRATEGIES**

Beyond oral SERDs, other novel ER-targeting drug designs have been developed in an effort to overcome endocrine resistance. H3B-6545 is a first-in-class selective ER covalent antagonist (SERCA) being developed by H3 Biomedicines. It binds covalently to a cysteine residue present in both the wild-type and mutant ER and induces an irreversible antagonistic conformation in a manner that is distinct from that of SERMs and SERDs.20

As of February 2020, 130 patients had been enrolled in the dose-escalation (100-600 mg once daily) and dose-expansion (450 mg once daily) parts of an ongoing phase 1/2 clinical trial (NCT03250676) of H3B-6545 in pre-or postmenopausal women with previously treated advanced breast cancer. Fifty-eight percent of patients had ESR1 mutations.

Among 105 evaluable patients, 13 had confirmed PRs, 11 of which were in patients treated with the 450-mg dose. Investigators reported 3 PRs in the 12 patients with the ESR1 Y537S mutation. In addition, H3B-6545 demonstrated a manageable safety profile.21

PROTACs are targeted protein degraders pioneered by Arvinas, a clinical-stage biopharmaceutical company founded by the Yale University investigators who developed the technology.22

ARV-471 is a PROTAC in which estradiol, an estrogen hormone, is linked to a small-molecule ubiquitin E3 ligase-binding moiety. This drug is designed to facilitate an interaction between the ER and an E3 ligase complex that will tag the ER for degradation by the ubiquitin-proteasome system.4,23

In a December 2020 press release, Arvinas detailed interim findings from a phase 1 clinical trial of ARV-471 (NCT04072952). As of November 2020, 21 patients had completed at least 1 treatment cycle. They were heavily pretreated, with a median of 5 prior lines of therapy. The findings included 1 confirmed PR, 2 unconfirmed PRs, and a CBR of 42%. The most common TRAEs were nausea, arthralgia, fatigue, and decreased appetite; all were grade 1 or 2. A cohort expansion in which ARV-471 is administered in combination with palbociclib is ongoing.24
ALTHOUGH TRASTUZUMAB (HERCEPTIN)-BASED regimens remain the standard treatment for patients with early-stage HER2-positive breast cancer, unanswered clinical questions surround the use of other agents in the neoadjuvant and adjuvant settings. With several options on the table, risk-adapted approaches to therapy have paved the way for personalized medicine and the opportunity to move away from therapies with higher toxicity profiles, such as anthracyclines.

“The debates that are going on are what’s the appropriate chemotherapy backbone and do you need an anthracycline, for example?” Lisa A. Carey, MD, said during a recent OncLive Peer Exchange®. “What’s the extent to which we need all those drugs, and can we rationally optimize therapy even for patients at higher clinical risk?”

A panel of breast cancer experts examined neoadjuvant and adjuvant systemic therapy approaches for patients with HER2-positive early-stage breast cancer. They also unpacked key updates to clinical trial data and shared how these affect their decision-making.

**REEXAMINING NEOADJUVANT STANDARDS OF CARE**

“We’re treating the majority of patients with HER2-positive breast cancer in the neoadjuvant setting. They’re getting their chemotherapy and anti-HER2 targeting preoperatively, for the most part, and then [postoperative] HER2 targeting is predicated on extent of disease that’s found at surgery,” Carey said, noting this approach has shown several benefits. “You can create more lobectomy candidates and can reduce the need for axillary dissection.”

It also enables oncologists to see how responsive a patient’s tumor is to their neoadjuvant regimen, enabling better tailoring of postoperative adjuvant treatment. For example, in the KATHERINE trial (NCT01772472), adjuvant ado-trastuzumab emtansine (Kadcyla; T-DM1) was associated with better outcomes than trastuzumab alone in patients who had residual invasive disease after completing neoadjuvant therapy.¹

A key ongoing question for patients with HER2-positive disease is which neoadjuvant regimen is best. In the preoperative setting, Carey said she typically uses TCH (docetaxel [Taxotere], carboplatin, trastuzumab), adding pertuzumab (Perjeta) for patients with node-positive disease, but not for those with node-negative disease, per the APHINITY trial (NCT01358877) data. Six-year follow-up data showed patients who were node-positive continued to derive a benefit from the addition of pertuzumab, demonstrating a 4.5% absolute improvement in invasive disease–free survival, regardless of their hormone receptor status.²

¹ I shifted a little while ago more toward TCHP [docetaxel, trastuzumab,
pertuzumab, carboplatin], although I do find that it’s a difficult regimen,” Claudine Isaacs, MD, said. “From a symptom-control perspective, it’s one of the toughest regimens we give.”

Overall, the participants agreed that they no longer use anthracyclines as they once did. “The TRAIN-2 data were further evidence for us that the anthracyclines really didn’t add much,” Isaacs said. The phase 3 TRAIN-2 study (NCT01996267) looked at chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2-positive breast cancer.³ Three-year follow-up showed an estimated event-free survival of 92.7% for the anthracycline cohort versus 93.6% in the nonanthracycline cohort, with 3-year overall survival (OS) estimates of 97.7% and 98.2%, respectively. Two patients in the anthracycline cohort developed acute leukemia. These findings confirmed the results of the primary outcome analysis, which was that anthracyclines do not improve treatment efficacy and are associated with clinically relevant toxicity.³

Despite these data, Vijayakrishna Gadi, MD, PhD, noted that some patients in his practice who are HER2-positive still receive anthracyclines. “For patients who have substantial burden of disease—maybe somebody who has not been [screened] but walks in with a big mass—I frequently start with the taxane portion, and then I’m on the fence a little on the anthracycline, [but] most of those patients still end up [receiving] the anthracycline in my practice,” he said. “There are always going to be patients whose circumstances are different, where you think you need to escalate in that direction and offer more with an anthracycline or what have you,” he explained.

Moderator Joyce A. O’Shaughnessy, MD, added that part of the concern about relying on TRAIN-2 data regarding the role of anthracyclines is that it is a relatively small trial with fewer than 500 patients. Nevertheless, she said, the data are still encouraging because they show it is possible to move away from anthracyclines, which should be the ultimate goal.

**IDENTIFYING AND TREATING PATIENTS AT HIGH RISK OF RECURRENCE AFTER NEOADJUVANT THERAPY**

“In my mind, the fundamental thing that defines risk after receiving neoadjuvant therapy is what the residual disease burden looks like. If there’s significant disease, particularly in nodes, that would be very worrisome, as it would be if there’s a significant amount of disease in the breast,” William J. Gradishar, MD, said. He also noted that anyone who progresses while on neoadjuvant therapy would be considered high risk but said this is not something he has frequently observed.

The participants agreed that T-DMI is the standard of care for patients with residual disease after TCHP or AC-THP (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab). "Most patients do OK with it, so I would try to leverage that benefit that we saw in KATHERINE and confer [it on] whoever has residual disease," he said.

Gadi said he struggles a bit with treatment decision-making when it comes to patients who are node-positive and achieve a pathologic complete response (pCR). “You look at some of the trials, and you start picking at them a little. There seems to be a suggestion that maybe you should continue the [trastuzumab and pertuzumab]. I have to be honest; I don’t find that data compelling,” he said, noting that he often continues only the trastuzumab and not the pertuzumab in these patients.

“I don’t think we know the right thing to do,” Carey said. She added that if she observed a pCR out of a trastuzumab/pertuzumab–based regimen, her tendency would be to continue the combination. Isaacs agreed. “I tend to continue trastuzumab and pertuzumab, as well, if somebody is tolerating it and there’s no compelling reason to stop it,” she said.

O’Shaughnessy mentioned that the FDA label for pertuzumab is interesting because it indicates that if this agent is used preoperatively, it should be continued for 1 year postoperatively. The label states, “Following surgery, patients should continue to receive [pertuzumab] and trastuzumab or trastuzumab/hyaluronidase-oysk [Herceptin Hylecta] to complete 1 year of treatment (up to 18 cycles).”⁴ However, she noted that it is still unclear whether this is necessary. “If someone has a pCR, do they really need it?” she asked.

**ADJUVANT SYSTEMIC THERAPY: IMPLICATIONS OF DATA UPDATES**

The participants also discussed recent updates to key adjuvant therapy trials, including APHINITY, ExteNET, and KATHERINE, and shared how these data may affect clinical practice.

**APHINITY Trial**

Isaacs discussed a subpopulation treatment effect pattern plot (STEP) analysis of the APHINITY trial, which was presented at the 2020 San Antonio Breast Cancer Symposium Virtual Annual Meeting.⁵ “What came out was very much in keeping with what we thought, that the group that derived the greatest benefit were the patients who had higher clinical risk,” she said. In the study, patients with HER2-positive, node-positive early-stage breast cancer benefited the most from the addition of adjuvant pertuzumab (as compared with patients with node-negative early-stage breast cancer), with benefit seen irrespective of STEPP subpopulation; however, the largest gains were for patients with lower-risk node-positive disease and those with the highest number of tumor-infiltrating lymphocytes (TILs) (Table 1.5.6).

Isaacs noted that although the information on TILs is interesting, it is difficult to apply in practice. “We’re not necessarily getting TIL numbers when we’re getting path specimens on patients who are getting core biopsies,” she said. However, even without knowing patients’ TIL status, she noted the data further support current clinical practice regarding the use of adjuvant pertuzumab for patients with HER2-positive, early-stage breast cancer.
**TABLE. Select Data from Adjuvant Therapy Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Outcome</th>
<th>Node-positive subgroup analysis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APHINITY (NCT01358877):</strong> study of pertuzumab in addition to chemotherapy and trastuzumab as adjuvant therapy in patients with HER2-positive primary breast cancer.</td>
<td>6-year iDFS rate</td>
<td>Pertuzumab</td>
<td>87.9% (HR, 0.72; 95% CI, 0.59-0.87)</td>
<td>83.4%</td>
</tr>
<tr>
<td><strong>ExteNET (NCT00878709):</strong> study of neratinib after adjuvant trastuzumab in women with early-stage breast cancer.</td>
<td>5-year iDFS rate</td>
<td>Hormone receptor-positive who initiated treatment ≤ 1 year of completing prior trastuzumab subgroup analysis</td>
<td>Neratinib (n = 670)</td>
<td>90.8% (95% CI, 88.1%-93.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR, 0.58 (95% CI, 0.41-0.82)</td>
<td>85.7% (95% CI, 82.6%-88.3%)</td>
</tr>
<tr>
<td><strong>KATHERINE (NCT01772472):</strong> study examining T-DM1 versus trastuzumab as adjuvant therapy in patients with HER2-positive breast cancer who have residual tumor in the breast or axillary lymph nodes following preoperative therapy.</td>
<td>3-year iDFS rate</td>
<td>T-DM1 (n = 743)</td>
<td>88.3% (HR, 0.50; 95% CI, 0.39-0.64)</td>
<td>77.0%</td>
</tr>
</tbody>
</table>

iDFS, invasive disease-free survival.

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**ExteNET Trial**

Next, Isaacs reviewed the final OS analysis of the randomized phase 3 ExteNET trial (NCT00878709), which included 2840 patients with estrogen receptor (ER)-positive, HER2-positive early breast cancer who were treated with neratinib (Nerlynx) or placebo after neoadjuvant/adjuvant trastuzumab-based therapy. “There emerged a survival benefit [with neratinib]—an approximate 2% survival benefit—if you looked at the super-highest risk: the [patients who were] hormone receptor-positive who started within a year of completing their therapy, and the ones who didn’t achieve a pCR,” Isaacs said.

A challenge she noted is knowing where the drug fits in during the era of T-DM1 and pertuzumab. “In the really high-risk patients, particularly if they have hormone receptor-positive disease—and we all have some patients who have multiple nodes, 2 or 3 nodes—I do tend to give them neratinib,” she said.

Gadi said he has been using neratinib more frequently recently. “I believe that ER-positive disease is fundamentally different from the kind that’s ER negative. If we don’t address that cross talk, and we don’t do that with T-DM1, I’m still worried about these patients having events down the road,” he explained. He also noted that what makes neratinib appealing to him is its ability to cross the blood-brain barrier. “I know that trials are underpowered for CNS [central nervous system] as a first site of recurrent type event. It’s my suspicion that those are patients who are vulnerable to those events when you have residual disease, have done T-DM1, and have ER-positive disease. I’d like to give them that extra bit of coverage for that, as well as for prevention of those CNS events,” he said.

The challenge with neratinib, however, is its adverse effect profile, particularly diarrhea, which can make it difficult for patients to tolerate. Subsequently, Gradishar said he does not use it a lot, but he agreed that he would use it for patients such as Isaacs described, adding that patients and oncologists both need to be highly motivated for the patient to be able to get through this treatment. Because of this agent’s toxicities, O’Shaughnessy emphasized the importance of escalating it per the findings from the CONTROL trial (NCT02400476), which investigated antidiarrheal strategies in patients with early HER2-positive breast cancer treated with neratinib. In the study, both preemptive prophylaxis and dose escalation reduced the rate, severity, and duration of grade 3 diarrhea compared with the levels observed in ExteNET, but dose escalation was particularly promising, with only 3% of patients on this strategy discontinuing treatment due to diarrhea.

“In the CONTROL trial, they escalated relatively quickly, I was surprised...It was the most effective,” Carey said. She said when she has a patient whose cancer is very high risk, she sometimes uses neratinib. “I’ve been happier with the option of dose escalation,” she said.

**KATHERINE Trial**

Data from the KATHERINE trial showed that among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone. “I was really impressed by the KATHERINE data. The data showed this really big 3-year, invasive disease-free survival benefit for the patients who didn’t achieve a pCR [in the neoadjuvant setting]. It’s approximately an 11% absolute benefit,” Isaacs said.

Recently, exploratory analyses evaluating the relationship between invasive disease-free survival and biomarkers potentially related to response showed that PIK3CA mutation status did not influence outcomes with trastuzumab or T-DM1, and that T-DM1 benefit was not affected by any of the biomarkers assessed; however, HER2 and PD-L1 expression levels correlated with outcomes in the trastuzumab arm.

Based on the KATHERINE data, the American Society of Clinical Oncology recently updated its guidelines on the selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer. It now strongly recommends that patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy be offered 14 cycles of adjuvant trastuzumab emtansine, unless there is disease recurrence or unmanageable toxicity. The guidelines note that clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars.

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