New Frontier for Genomics: Radiotherapy in Early Breast Cancer

COVID-19: Community Practices Scramble to Respond

PEER EXCHANGE
HEMATOLOGIC MALIGNANCIES
Exciting Potential in Refractory DLBCL

OnePathways®
CML Research Aims to Improve a “Magic Bullet”

MIAMI BREAST CANCER CONFERENCE®
Experts Weigh In on Immunotherapy and ADCs

CLINICAL PERSPECTIVES
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on New HCC Care Model
Sonali M. Smith, MD,
on Upfront Options in iNHL
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on Cervical Cancer Palliative Care

WINTHROP P. ROCKEFELLER CANCER INSTITUTE
Controversy Surrounds Treatment of High-Risk Smoldering Myeloma
BY SHARMILAN THANENDRARAJAN, MD
The efficacy of XOSPATA was established on the basis of CR\textsuperscript{1}/CRh,\textsuperscript{2} the duration of CR/CRh (DOR), and the rate of conversion to transfusion independence at the first interim analysis\textsuperscript{1}.$^{\dagger}$ In the final analysis,\textsuperscript{1} XOSPATA delivered superior overall survival vs salvage chemotherapy\textsuperscript{1}:

<table>
<thead>
<tr>
<th>36% reduced risk of death with XOSPATA (n=247)</th>
<th>vs salvage chemotherapy (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 9.3 months median OS (95% CI: 7.7, 10.7)</td>
<td>vs 5.6 months with salvage chemotherapy (95% CI: 4.7, 7.3)</td>
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<tr>
<td>HR=0.64 (95% CI: 0.49, 0.83); P=0.0004</td>
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$^{\dagger}$ 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 prespecified salvage chemotherapy regimen.\textsuperscript{1}

$^{1}$CR defined as normal marrow differential with <5\% blasts, ANC $\geq$1.0 x 10\(^9\)/L and platelets $\geq$100 x 10\(^9\)/L, no evidence of extramedullary leukemia, and must have been RBC and platelet transfusion independent.\textsuperscript{1}

$^{2}$CRh defined as marrow blasts <2\%, partial hematologic recovery, ANC $\geq$0.5 x 10\(^9\)/L and platelets $\geq$50 x 10\(^9\)/L, no evidence of extramedullary leukemia, and could not have been classified as CR.\textsuperscript{1}

$^{3}$Response was ongoing.\textsuperscript{1}

*FLT3 mutation status: FLT3-ITD, FLT3-TKD, and FLT3-ITD-TKD.\textsuperscript{1}

XOSPATA is the First Oral Monotherapy to Deliver Superior Overall Survival vs Salvage Chemotherapy in Relapsed or Refractory FLT3\textsuperscript{m+} AML\textsuperscript{1}$^{\ast}$

**Gilteritinib (XOSPATA) is the ONLY Category 1 recommendation for patients with relapsed or refractory AML with a FLT3 mutation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)\textsuperscript{2}**

- XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in 371 adult patients with relapsed or refractory FLT3\textsuperscript{m+} AML.\textsuperscript{1,3}
- The efficacy of XOSPATA was based on an interim analysis and a final analysis\textsuperscript{1}:
  - The first interim analysis evaluated the endpoints of CR/CRh, the DOR, and the rate of conversion from transfusion dependence to transfusion independence in 138 patients treated with XOSPATA
  - The final analysis evaluated the endpoint of OS and was measured from the date of randomization until death by any cause

$^{\ast}$References: 1. XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Myeloid Leukemia V.3.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed 01-29-2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Astellas. XOSPATA. Data on File.

Please see adjacent pages for Brief Summary of Full Prescribing Information, including BOXED WARNING.
**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.

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**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 symptoms resolve.

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**Warnings and Precautions**

**Differentiation Syndrome (See Boxed Warning)**

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

**Posterior Reversible Encephalopathy Syndrome (PRES)**

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

**Prolonged QT Interval**

XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or 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/arthritis (7%), and fatigue/malaise (6%).

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

**Lab Abnormalities**

Shifts to grades 3-4 nonhematological 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.

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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.

DOSAGE 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 chemistry, 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.

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

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

ADVERSE REACTIONS

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

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

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These included cardiac arrest (1%) and one case 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/arthralgia (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%).

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

Shots 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, dermatis allergic, drug hypersensitivity, erythema multiforme, hypersensitivity, and urticaria), pancreatitis (amylose increased, lipase increased, pancreatitis, pancreatitis acute), pericarditis/myocarditis (myocarditis, pericardial hemorrhage, pericardial rub, and pericarditis).

DRUG INTERACTIONS

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.

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 days 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.

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<td>Charles A. Sammons Cancer Center</td>
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<td>UTSouthwestern</td>
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**OncologyLive**

Vol. 21 / No. 8 / APRIL 2020

www.OncLive.com

New Frontier for Genomics: Radiotherapy in Early Breast Cancer

by TERRY P. MAMOUNAS, MD, MPH; MELISSA P. MITCHELL, MD, PHD; and WENDY A. WOODWARD, MD, PHD

Although genomic assays have helped refine predictions for the risk of distant recurrence for patients with early breast cancer, the treatment model for locoregional disease still relies upon the evaluation of clinical features. The use of genomic profiling in this setting looks promising, but it’s not yet ready for prime time, say these experts in the field.

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By Denise Myshko

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Cancer hits hard in Kentucky. That’s why, every day, the team at Markey steps up, with innovative clinical trials to help treat diseases like aggressive colon cancer. Those types of trials mean more patients in remission and the potential to help others all over the world—because we’re not just treating cancer today. We’re working hard to beat it once and for all.

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ALTHOUGH WELL-ESTABLISHED biomarkers for hormonal, HER2 and BRCA status exist to guide treatment decisions for patients with breast cancer, the clinical utility of genomic testing represents a dynamic and exciting area of current and future exploration.

In 2018, Sparano et al reported that the 21-tumor gene expression assay Oncotype DX can help predict the need for adjuvant chemotherapy after primary surgery for women with hormone receptor–positive, HER2-negative, node-negative, early-stage breast cancer.1

Results of the phase III TAILORx study (NCT00310180) suggest that the assay “may identify up to 85% of women with early breast cancer who can be spared adjuvant chemotherapy,” Sparano and colleagues wrote. Data from the large, prospective study, which recruited 10,273 participants, may be particularly helpful for patients with intermediate risk of recurrence scores (defined as 11 to 25 out of 100).1

The oncology community widely hailed those findings for the impact that a more detailed understanding of recurrence risk may have on the lives of patients with one of the most common types of breast cancer. Notably, however, similar efforts are under way to determine whether genomic classifiers can also be developed to better predict which patients with early-stage breast cancer would benefit from radiation therapy.

In this issue of OncologyLive®, we feature a thorough exploration of the potential for genomic profiling data to prove useful in determining the course of locoregional treatment for this population. The article is written by leading breast cancer experts Terry P. Mamounas, MD, MPH; Melissa P. Mitchell, MD, PhD; and Wendy A. Woodward, MD, PhD.

The authors describe intriguing data associating gene expression profiling and molecular subtyping with prognostic and predictive capabilities of radiation therapy in several localized treatment settings. However, they conclude that further studies are needed to establish algorithms that can be translated into clinical practice. Fortunately, investigators are conducting several such studies.

Although genomic studies are lengthy and painstaking undertakings, the work of determining the practical uses for information gleaned from tumor profiling is vitally important. The complexity in identifying which subgroups of patients may benefit from specific strategies is the essence of personalized medicine.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCE

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The primary role of surgery in the management of malignant disease is indisputable. This modality has been central to the fundamental success of oncology therapeutics from the earliest days of cancer treatment, when essentially the only valid option for cure or palliation was surgical removal of a mass or masses (“solid tumors”), until today, when ever-improving imaging techniques and experience have strikingly refined the extent of such surgical resections. All one has to do is consider the remarkable evolution of the standard-of-care curative approach in the management of breast cancer to appreciate the magnitude of changes in surgical oncologic strategies; the field has moved from the historical Halsted radical mastectomy to the far less morbid lumpectomy followed by external beam radiation.

In recognition of the foundational and impressively evolving role of surgery in cancer management, the American Society of Clinical Oncology (ASCO) named “refinement of surgical treatment of cancer” as its Advance of the Year for 2020. The ASCO report highlighted examples of highly relevant changes in the surgical approach that have fundamentally and positively affected outcomes and quality of life for patients with cancer.

The administration of neoadjuvant cytotoxic chemotherapy in several clinical settings has permitted subsequent surgical intervention to remove a primary malignancy, as in breast cancer, or safely and effectively cytoreduce residual macroscopic tumors, as in ovarian cancer. Increasingly effective targeted therapy in certain clinical settings, such as renal cell cancer and melanoma, has permitted systemic therapy to become the primary treatment modality, with surgery employed to remove partially responsive tumor masses or residual disease unresponsive to an antineoplastic regimen. Initial systemic or local radiation therapy may also permit resection of a locally advanced primary malignancy, as in pancreatic cancer. Finally, the delivery of systemic therapy or local radiation therapy may also permit less extensive but equally effective curative resections, such as in the case of limb sarcomas in children and adults.

Of course, these highly relevant clinical advances are critically informed by the conduct of prospective clinical trials, or the publication of analyses of prospective or retrospective experiences at single or multiple centers with expertise in surgical oncology.

Differences in modalities
Although surgical, radiation, and systemic treatment strategies are all important in cancer management, there are fundamental and pragmatic differences between these concepts within the clinical trial domain and ultimately in routine clinical practice. Although the inherent biology of an individual cancer may ultimately trump the ability of any modality to favorably influence the natural history of that malignancy, the impact that the oncology specialist has on cancer-specific and overall outcomes may vary greatly depending on the modality.

Consider an example—admittedly somewhat extreme—that highlights the point of this commentary. If an internationally recognized expert in the antineoplastic drug management of “cancer A” orders standard-of-care “treatment B” for “patient C,” there is absolutely no reason to believe that the biological or clinical response to treatment, such as shrinkage of the tumor mass or masses, reduction in tumor markers, or improvement in cancer-related symptoms, would be different if the same regimen were ordered by a first-year medical oncology trainee during the first day of her/his fellowship.

In striking contrast, no one would make such an outlandish claim that outcomes would be equivalent for a surgical oncologist with several decades of experience in managing a specific cancer type compared with a surgical resident during her/his first year or day of training. In this situation, the combined experience of a given surgical team and hospital in dealing with such complex surgeries also should be considered.

Unique Aspects of Cancer Surgery Make Clinical Trials Challenging

by MAURIE MARKMAN, MD

The primary role of surgery in the management of malignant disease is indisputable. This modality has been central to the fundamental success of oncology therapeutics from the earliest days of cancer treatment, when essentially the only valid option for cure or palliation was surgical removal of a mass or masses (“solid tumors”), until today, when ever-improving imaging techniques and experience have strikingly refined the extent of such surgical resections. All one has to do is consider the remarkable evolution of the standard-of-care curative approach in the management of breast cancer to appreciate the magnitude of changes in surgical oncologic strategies; the field has moved from the historical Halsted radical mastectomy to the far less morbid lumpectomy followed by external beam radiation.

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From the Editor

Again, although these scenarios may be a bit extreme, the point is clear: Cancer surgery, especially complex procedures undertaken in advanced or difficult circumstances as well as innovative procedures such as robotic surgery, demands knowledge, particular skills, and experience to optimize the opportunities for the most favorable possible clinical outcomes.

As a result, the conduct of randomized trials in surgical oncology, although highly appealing in concept, may be problematic, especially in complex settings where the skills, experience, and clinical judgment of individual surgeons and their institutions may vary greatly.

It is common to hear surgeons described by their surgical and nonsurgical colleagues as being "aggressive" or "conservative" in their basic approach to management within the operating room. Without passing judgment on any surgical philosophy, we can consider the question of whether such perspectives, along with the previously noted characteristics of skill and experience, might affect the results of a cancer trial in the surgical domain.

AN ATTEMPT AT OBJECTIVE CRITERIA

In an interesting and provocative report, Japanese investigators have attempted to assess objectively the relationship between certain outcomes and the surgeon’s experience and ability to undertake complex surgery for gynecologic cancers.¹ They evaluated operative time and total blood loss in a consecutive population of ovarian cancer surgeries (N = 271) performed only by gynecologic oncologists and divided the procedures into 2 categories of complexity. The investigators found that approximately 50 operations were required before proficiency was achieved in high-complexity cases. Not surprisingly, a lower number of total cases was required for an individual surgeon to be classified as being proficient in less-complex surgeries.

Of course, there is nothing magical about 50 cases or any other number of procedures that would define the necessary experience for a given surgeon to be able to successfully undertake a case and achieve an optimal clinical outcome, including operative and postoperative morbidity and mortality.

However, it is important to appreciate the unique relevance of such skills and experience in the design and interpretation of surgical clinical trials in oncology and in reports of outcomes from individual institutions and groups. Further, this heterogeneity in surgical providers may help at least partially explain different conclusions that have been reached regarding the impact of innovative surgical strategies on clinical outcomes, such as minimally invasive radical surgery in the management of cervical cancer.² ³ ⁴

REFERENCES

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

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

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

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

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

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria occurred in 7% of CABOMETYX patients. Monitor Proteinuria occurred in 7% of CABOMETYX patients. Monitor Proteinuria regularly during CABOMETYX treatment. Withhold CABOMETYX for development of ONJ until complete resolution. Monitor patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 proteinuria.

ONJ occurred in <1% of CABOMETYX patients. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Grade 3 or 4 proteinuria occurred in 1% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Diabetes and Demyelination: Diabetes mellitus occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms of diabetes mellitus. Discontinue CABOMETYX in patients who develop diabetes mellitus.

Demyelination occurred with CABOMETYX. Monitor for signs and symptoms of demyelination. Discontinue CABOMETYX in patients who develop demyelination.

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

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

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

ADVERSE REACTIONS
The most commonly reported (>25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.

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

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

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

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.
5.8 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

5.9 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

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

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

4.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 63% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Proteinuria
Proteinuria was observed in 7% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Table 1. Adverse Reactions Occurring in ≥ 10% of Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (%) of Patients</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Anemia</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td>Rash</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Vascular</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Metabolic and Nutrition</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Mucosal</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculoskeletal and Connective tissue</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
22% of patients receiving sunitinib discontinued due to disposition, 21% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was reduced in 46% of patients receiving CABOMETYX and 44.7 mg for sunitinib (excluding decreased ALT, decreased appetite, stomatitis, pain, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, hypotension, and syncope.

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
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<tr>
<td>Increased AST</td>
<td>74</td>
<td>3</td>
<td>40</td>
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<tr>
<td>Increased ALT</td>
<td>68</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>53</td>
<td>4</td>
<td>73</td>
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<tr>
<td>Hypochromatemia</td>
<td>48</td>
<td>8</td>
<td>36</td>
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<tr>
<td>Hyperglycemia</td>
<td>2</td>
<td>5</td>
<td>9</td>
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<td>Hyperuricemia</td>
<td>36</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Increased RBC</td>
<td>35</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>31</td>
<td>7</td>
<td>4</td>
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<tr>
<td>Hypothyroidism</td>
<td>30</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Increased GGT</td>
<td>27</td>
<td>5</td>
<td>43</td>
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<tr>
<td>Hematology</td>
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<td></td>
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<tr>
<td>Leukopenia</td>
<td>31</td>
<td>&lt;1</td>
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<tr>
<td>Neutropenia</td>
<td>31</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>4</td>
<td>71</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>25</td>
<td>7</td>
<td>39</td>
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<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>&lt;1</td>
<td>27</td>
</tr>
</tbody>
</table>

Potential for CABOMETYX-Treated Patients in CELESTIAL

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=78)</th>
<th>Sunitinib (n=72)</th>
<th>Grade 3-4</th>
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Hepatobiliary Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatobiliary carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.6 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatoportal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 53% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).
In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerular hyperplasia), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner’s gland and inflammation of duodenum; epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and inflammation of duodenum; and epithelial hyperplasia of colon and cecum). No developmental effects were reported in juvenile rats administered cabozantinib to postnatal day 20. Cabozantinib did not produce adverse effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.5 Geriatric Use

In CAISUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 46% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older.

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSE

One case of overdose was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 creatine disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage. Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistulas have been reported in patients taking CABOMETYX. Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolism have been reported. Advise patients to contact their healthcare provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

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

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

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

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

Thrombotic events: Venous and arterial thrombotic events including pulmonary embolism have been reported. Advise patients to seek immediate medical attention for signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolism have been reported. Advise patients to contact their healthcare provider for progressive or intolerable rash.

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Durvalumab Scores Approval for Frontline Treatment of ES-SCLC

Durvalumab (Imfinzi) is now cleared for use as a frontline therapy for adults with extensive-stage small cell lung cancer (ES-SCLC) in combination with standard-of-care chemotherapy including etoposide with either carboplatin or cisplatin.

The agent’s approval is based on findings from the phase III CASPIAN trial (NCT03043872), which showed that durvalumab and chemotherapy reduced the risk of death by 27% compared with chemotherapy alone (HR, 0.73; 95% CI, 0.591–0.909; P = .0047). The median overall survival was 13.0 months (95% CI, 11.5–14.8) with the doublet regimen versus 10.3 months with etoposide and platinum chemotherapy.

Additionally, the objective response rates were 68% and 58% for the durvalumab arm and chemotherapy-only group, respectively, representing a 56% increase in the likelihood of response with the addition of durvalumab.

Avapritinib Could See Expanded Indication in GIST

Just months following its initial approval in gastrointestinal stromal tumor (GIST), avapritinib (Ayvakit) is moving toward another indication. The kinase inhibitor is now undergoing a priority review for adults with fourth-line GIST; the FDA is scheduled to issue a decision on the agent’s new drug application by May 14, 2020.

In January 2020, the FDA approved avapritinib for adults with unresectable or metastatic GIST who harbor a PDGFRα exon 18 mutation, including PDGFRα D842V alterations, after the therapy demonstrated its efficacy in the phase I NAVIGATOR trial (NCT02508532). In the cohort of patients with fourth-line disease (n = 121), the objective response rate was 22% (95% CI, 14.4–30.4), with 1 complete response and 23 partial responses. Additionally, 52 patients had stable disease, investigators said.

At a follow-up of 10.8 months, the median duration of response was 10.2 months (95% CI, 7.2-not estimable) and the median progression-free survival was 3.7 months (95% CI, 3.4–5.6). The clinical benefit rate was 41%.

FDA Agrees to Review Bevacizumab Biosimilar Application

The FDA has accepted a biologics license application (BLA) for MYL-1402O, a proposed biosimilar for bevacizumab (Avastin). If approved, MYL-1402O would be the third bevacizumab biosimilar cleared for use in oncology, following bevacizumab-awwb (Mvasi) and bevacizumab-bvzr (Zirabev), both of which launched in the United States in 2019. The FDA will issue a decision on MYL-1402O by December 27, 2020.

MYL-1402O’s BLA included results from a comprehensive data package that demonstrated biosimilarity between the agent and reference bevacizumab. This biosimilarity was consistently upheld through analytical, pharmacokinetic, and pharmacodynamic studies, as well as in a phase I study (NCT02469987) of MYL-1402O in 111 patients with metastatic colorectal cancer.

The treatment-emergent adverse events (TEAEs) observed with the biosimilar in this trial were consistent with prior findings in clinical investigations of bevacizumab, and no serious or unexpected TEAEs were reported, investigators said.

The drug, which is being codeveloped by Mylan and Biocon, was approved by the Drug Controller General of India in November 2017 for all indications of reference bevacizumab.
Drug Spotlight | Neratinib (Nerlynx)

Application of Neratinib in Breast Cancer Broadens

by Rachel Narozniak, MA

The recent approval of neratinib (Nerlynx) in combination with capecitabine (Xeloda) for patients with late-stage, heavily pretreated HER2-positive breast cancer expanded the therapy’s established role in this disease setting.

Neratinib was initially approved in July 2017 for the extended adjuvant treatment of adults with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab (Herceptin)-based therapy.1

The latest approval is based on efficacy results from the phase III NALA trial (NCT01808573), which showed that treatment with the doublet therapy not only significantly improved progression-free survival (PFS) but also trended toward an overall survival benefit among those who received the combination. At 12 months, the PFS rate was 29% (95% CI, 23%-35%) with neratinib and capecitabine versus 15% (95% CI, 10%-20%) with lapatinib (Tykerb) and capecitabine.1

In an interview with OncologyLive®, Adam M. Brufsky, MD, PhD, FACP, codirector of the Comprehensive Breast Cancer Center and associate chief of the Division of Hematology/Oncology at the University of Pittsburgh Medical Center Hillman Cancer Center in Pennsylvania discussed neratinib and the importance of expanding the treatment portfolio in HER2-positive metastatic breast cancer.

Can you discuss the pivotal efficacy data that led to the approval?

There were a few interesting things about this trial. Some are subtle and some are not, but the bottom line is that the NALA trial showed efficacy. The trial’s primary end point was progression-free survival, and it met that end point in an unusual way. This is where it gets a little bit complicated: The survival curve separated late, after about 6 months. I think most likely they separated later [in the trial] because there were probably fewer progressions of brain metastases.

The progression-free survival was 8.8 months in the neratinib and capecitabine arm and 6.6 months in the lapatinib and capecitabine arm. The overall survival benefit was about a month and a half, on average, and it was not statistically significant. What was interesting, though, was that the duration of response almost doubled. What was also interesting was that, unlike the HER2CLIMB study [NCT02614794] of tucatinib—which is a similar agent but does not induce diarrhea [as frequently as neratinib]—we did not require an MRI [magnetic resonance imaging] at baseline. Only about 20% of the patients in our study had brain metastases, but we did not really know that, so we looked to see who required symptomatic intervention for brain metastases to estimate who had brain benefit.

As it turns out, about 30% in the lapatinib and capecitabine arm required a symptomatic intervention for brain metastases versus about 22% in the neratinib and capecitabine arm. That is an improvement in absolute terms of about 8% and of about 25% to 30% in relevant terms. In trying to understand the data, I think neratinib, which is an irreversible binder to HER2, will cross the blood-brain barrier, get onto the brain metastasis, and stick. It will not come off. In contrast, lapatinib is a reversible binder and could come back off because it is reversible. To me, that probably explains a lot of the benefit of neratinib in these patients.

What is the agent’s mechanism of action?

Neratinib blocks the HER2 receptors on the cell surface that dimerize with another protein called HER3. When that happens, the internal part of the receptor called the tyrosine kinase domain is activated. A lot of these small molecules like neratinib and lapatinib bind to the HER2 tyrosine kinase domain and block it from being activated. Neratinib is an irreversible binder that prevents the HER2 signal from being transmitted to the rest of the cell.

How does the agent fit into the current treatment paradigm?

In HER2-positive disease, we have fam-trastuzumab deruxtecan-nxki [Enhertu], which was approved in January. Trastuzumab deruxtecan is very powerful and seems to work pretty well, but we are not sure if it gets into the brain. However, neratinib does get into the brain.

There is a competitor to neratinib that will likely get FDA approval—tucatinib. With the [ongoing] pandemic, we are unsure when that is going to happen; we thought it would probably come over the summer. Tucatinib has the same affinity for the HER2 receptor as neratinib, but the difference between the 2 is that tucatinib does not bind to the epidermal growth factor receptor, and that is why there is a lot less diarrhea. We have a lot of ways now to manage the diarrhea, and with dose escalation of the neratinib starting at 150 or 160 mg a day and using anti-diarrhea pills like loperamide when escalating the dose, we actually reduce the incidence of severe diarrhea to single digits.

Another drug that has been tested is margetuximab, which is a reengineered HER2 receptor developed to have more of an immune response. The theory is that if there is more of an immune response to the receptor, it will synergize with trastuzumab to potentially kill more cells, and it will do so by better interacting with a receptor on the surface of natural killer cells.

Margetuximab was tested in the phase III SOPHIA trial [NCT02492711]. Although there was a progression-free survival benefit with margetuximab, there was not an overall survival benefit. The trial needed to reach both end points to be declared successful, so right now, margetuximab is in a bit of limbo because we are not quite sure whether [those data will] be enough for the FDA to approve it. It is an interesting drug, and we have a lot of trials that are going to be done with it now going forward, especially in the early setting including neoadjuvant therapy.

What does the approval of neratinib mean for this disease setting?

I think the overall summary of this entire field is that we did not have a lot of options for the second or third line and beyond for patients with HER2-positive metastatic breast cancer. Right now, the point estimate is a little under 5 years survival. In the CLEOPATRA trial [NCT00567190] of frontline pertuzumab [Perjeta], trastuzumab, and docetaxel for HER2-positive metastatic breast cancer, the median overall survival was 56.5 months, but interestingly enough, a third of the women were still alive 8 years later. What we want to do now is make that number 50% or 60% at this 8-year mark, and we can start to do that. Then I think you will start to see the natural history of this disease really make a change. I think we have done that already, but these agents are going to push it even further. That is why the approval of neratinib is so exciting.

Reference


Adam M. Brufsky, MD, PhD, FACP

Q Can you discuss the pivotal efficacy data that led to the approval?

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PHOTO COURTESY OF BLUEPRINT MEDICINES CORPORATION.

FDA approval—February 25, 2020

FDA grants approval for the kinase inhibitor neratinib (Nerlynx) in combination with capecitabine for adults with advanced or metastatic HER2-positive breast cancer who have received ≥2 anti–HER2-based regimens in the metastatic setting. Neratinib monotherapy was initially approved in 2017 for the extended adjuvant treatment of adults with early-stage HER2-overexpressed breast cancer, to follow adjuvant trastuzumab (Herceptin)–based therapy.

Mechanism of action:

- Neratinib is an intracellular kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4.
- In vitro, neratinib reduced EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and demonstrated antitumor activity in EGFR- and/or HER2-expressing carcinoma cell lines.
- In vivo, oral neratinib stymied tumor growth in mouse xenograft models with HER2- and EGFR-expressing tumor cell lines.

How supplied:

- 40-mg tablets

Dosing:

- 240 mg (6 tablets) given orally once daily with food on days 1 to 21 of a 21-day cycle plus capecitabine (750 mg/m2 given orally twice daily) on days 1 to 14 of a 21-day cycle until disease progression or unacceptable toxicities

Company: Puma Biotechnology, Inc

PIVOTAL EFFICACY DATA FOR APPROVAL

NALA (NCT01808573), a multicenter, open-label phase III study that enrolled 621 patients with stage IV HER2-positive metastatic breast cancer who had received ≥2 prior HER2-directed regimens for metastatic disease

Efficacy Population (N = 621)

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Efficacy Results for Approval in the NALA Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Neratinib and Capecitabine (n = 307)</th>
<th>Lapatinib and Capecitabine (n = 314)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.6 (4.9-6.9)</td>
<td>5.5 (4.3-5.6)</td>
<td>0.76 (0.63-0.93)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>21.0 (17.7-23.8)</td>
<td>18.7 (15.5-21.2)</td>
<td>0.88 (0.72-1.07)</td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>32.8% (27.1%-38.9%)</td>
<td>26.7% (21.5%-32.4%)</td>
<td></td>
</tr>
<tr>
<td>Duration of response, median months (95% CI)</td>
<td>8.5 (5.6-11.2)</td>
<td>5.6 (4.2-6.4)</td>
<td></td>
</tr>
</tbody>
</table>

ORR indicates objective response rate; OS, overall survival; PFS, progression-free survival.

WARNINGS AND PRECAUTIONS

- **Diarrhea:** Manage diarrhea that occurs despite prophylaxis with additional antidiarrheals, fluids, and electrolytes. Withhold neratinib in patients experiencing severe and/or persistent diarrhea. Permanently discontinue in patients with grade 4 or grade ≥2 diarrhea after maximal dose reduction.
- **Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months for the duration of treatment. Withhold neratinib in patients with grade 3 liver abnormalities; permanently discontinue in patients with grade 4 aberrances.
- **Embryo-fetal toxicity:** Neratinib can cause fetal harm. Advise patients of the potential risk to a fetus and encourage use of effective contraception.

COMMONLY REPORTED ADVERSE EVENTS IN NALA SAFETY POPULATION

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Neratinib and Capecitabine (n = 303)</th>
<th>Lapatinib and Capecitabine (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>83%</td>
<td>25%</td>
</tr>
<tr>
<td>Nausea</td>
<td>53%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>46%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>31%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>20%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Back pain</td>
<td>10%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

HR indicates hormone receptor; MBC, metastatic breast cancer.

REFERENCES


IN EARLY-STAGE BREAST CANCER, molecular subtyping and gene expression profiling has improved our ability to estimate risk of distant recurrence above and beyond traditional clinicopathologic factors and biomarkers.1-7 Despite this considerable progress in refining risk of distant recurrence, risk assessment for locoregional recurrence (LRR) is still primarily based on traditional clinicopathologic factors such as patient age, tumor size, grade, pathologic nodal status, presence of lymphovascular space invasion, and margin width.8,9

In addition, several studies have shown that tumor subtype alone is strongly predictive of LRR.5,10-16 Given the solid correlation between the risk of LRR and distant recurrence,17-19 several investigators have examined whether genomic assays that predict risk of distant recurrence can also predict risk of LRR.20-28 Increasingly, new genomic classifiers are being developed specific to LRR, in patients with node-negative and node-positive invasive breast cancer.29,30 There is also increasing interest in developing gene expression assays to predict response to radiation therapy (XRT).30-39

CAN GENOMIC PROFILING AFFECT THE SURGICAL MANAGEMENT IN THE BREAST OR AXILLA?

Local recurrence is also strongly influenced by the surgical approach. To date, molecular subtyping/genomic profiling has very little to no influence on the extent of surgical therapy, which is traditionally based on the anatomic extent of the tumor and not on underlying tumor biology. Anatomic extent of the tumor in the breast and axilla can be reduced by neoadjuvant therapy, which results in tailoring of the surgical approach. However, in the traditional model of surgery first followed by adjuvant systemic therapy, genomic profiling has very little influence on the extent of surgical therapy.

CAN GENOMIC PROFILING AFFECT THE USE OF ADJUVANT XRT?

By individualizing risk of LRR with molecular subtyping and use of genomic classifiers, it is hoped that use of adjuvant XRT can also be tailored. Currently, there are 2 approaches for tailoring use of XRT. First, is the potential of customizing the use of postmastectomy and regional nodal XRT. Second, is the potential of avoiding breast XRT in selected candidates at low risk of in-breast recurrence after breast-conserving surgery (BCS).

Adjuvant Postmastectomy and Regional Nodal Radiation Therapy

The association between the 21-gene recurrence score (RS) and risk of LRR has been evaluated in patients with node-negative, estrogen receptor (ER)–positive breast cancer treated with either no adjuvant therapy,
tamoxifen, or tamoxifen plus adjuvant chemotherapy as part of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and NSABP B-20 trials.40

Patients treated with BCS received breast XRT but patients who underwent a mastectomy received no XRT. RS was a significant predictor of LRR in all 3 groups of patients. In 895 patients treated with tamoxifen, the 10-year estimates of the proportion of patients with LRR were 4.3%, 7.2%, and 15.8% for patients with low, intermediate, and high RS, respectively (P <.001).

Similar association between RS and risk of LRR was identified in 424 patients treated with chemotherapy plus tamoxifen in the B-20 trial (10-year LRR rates: 1.6%, 2.7%, and 7.8% for patients with low, intermediate, and high RS, respectively, (P = .028)). This 5-fold difference in LRR between low versus high RS in patients treated with chemotherapy plus endocrine therapy is biologically interesting but has limited clinical implications for patients with node-negative disease relative to the potential need (or benefit from) postmastectomy or regional nodal XRT.

The previously mentioned observations of low LRR risk in patients with a low RS (<18) were recently confirmed in a large, contemporary cohort of patients with node-negative, ER-positive/HER2-negative breast cancer from Memorial Sloan Kettering Cancer Center in New York, New York.29 Most patients were treated with BCS plus XRT (66.6%) or total mastectomy alone (29.7%), endocrine therapy alone (84.8%), or chemo-endocrine therapy (12.1%). With a median follow-up of 52 months, the LRR rate was 0.9% overall and 0.7% in patients treated with adjuvant endocrine therapy only.

Similar findings have also been reported with other genomic classifiers. Fitzal et al evaluated the PAM50 assay in the ABCSG-8 trial of postmenopausal patients with ER-positive/HER2-negative disease, treated with endocrine therapy44; 21% of the patients had undergone a mastectomy. With a median follow-up of 11 years, the 10-year local recurrence-free survival (LRFS) risk was significantly associated with PAM50 risk of recurrence (ROR) (98.4% in the low/intermediate ROR group vs 94.4% in the high ROR group). ROR score was the only significant independent predictor of LRR in multivariate analysis. The groups that underwent breast conservation surgery and mastectomy had similar LRR rates (P = .879).

The significant association between genomic classifiers and LRR in patients with node-negative disease provided rationale for evaluating RS in those with node-positive disease, hoping that improved LRR stratification could help to tailor postmastectomy radiation therapy (PMRT) and/or regional nodal XRT use. Three studies have reported such an association based on retrospective assessment of RS in patients with exclusively node-negative breast cancer included in randomized clinical trials of adjuvant chemo-endocrine therapy (NSABP B-28, ECOG 2197, SWOG 8814).21,22,28

In the NSABP B-28 trial, patients with node-negative disease were randomized to doxorubicin/cyclophosphamide with or without paclitaxel. Patients aged ≥50 years and those aged <50 years with ER-positive and/or progesterone receptor–positive tumors also received tamoxifen. Patients treated with BCS received breast XRT but patients who underwent mastectomy did not receive XRT. RS was obtained in 1065 patients with ER-positive disease.22 With a median follow-up of 11.2 years, the 10-year cumulative incidence of LRR was 3.3%, 7.2%, and 12.3% for low, intermediate, and high RS, respectively (P <.001).

In multivariate regression analysis, RS remained an independent predictor of LRR (HR, 2.61 for a 50-point difference in RS; P = .008) along with pathologic nodal status (HR, 1.91 for ≥4 vs 1 to 3 positive nodes; P = .007) and tumor size (HR, 1.28 for a 1-cm difference; P = .015). Solin et al evaluated RS for prediction of LRR risk in BCS plus XRT-treated patients with 1 to 3 positive nodes in the ECOG E2197 study comparing 2 chemotherapy regimens.21

Table. Clinical Trials Evaluating Genomic Strategies for RT in Early Breast Cancer

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Study Description</th>
<th>Patient Population</th>
<th>Estimated Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTG MA.39</td>
<td>2 arms: • No regional RT; WBI after BCS or no RT after mastectomy</td>
<td>Women aged ≥40 years with HER2-negative, node-positive BC after BCS or mastectomy, defined as 1 to 3 positive axillary nodes with macrometastases &gt;2 mm; low-risk Oncotype DX RS (&lt;18)</td>
<td>2140</td>
</tr>
<tr>
<td>(TAILOR RT; NCT03488693)</td>
<td>• Regional RT: WBI + RT to regional nodes after BCS or RT to chest wall and regional nodes after mastectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUMINA (NCT01791829)*</td>
<td>Observational study evaluating risk of IBTR in patients receiving ET for 5 years without breast irradiation</td>
<td>Women aged ≥55 years with low-risk luminal A, ER-positive, HER2-negative invasive BC (ductal, tubular, or mucinous), defined as primary tumor ≤2 cm and negative axillary nodes after BCS</td>
<td>500</td>
</tr>
<tr>
<td>IDEA (NCT02400190)*</td>
<td>ET alone without RT</td>
<td>Postmenopausal women aged 50 to 69 years with hormone-sensitive, HER2-negative stage I (pT1NO) invasive breast cancer after BCS; low-risk Oncotype DX RS (≤18)</td>
<td>202</td>
</tr>
<tr>
<td>PRECISION (NCT02653755)</td>
<td>2 arms: • Ineligible for omission of RT: intermediate- or high-risk score • Eligible for omission of RT: Low-risk score; will receive ET</td>
<td>Women aged 50 to 75 years with ER-positive BC with negative lymph nodes and negative margins or re-excision following BCS for primary tumor ≤2 cm; stratified by Prosigna (PAM 50) score</td>
<td>690</td>
</tr>
<tr>
<td>EXPERT (NCT02889874)</td>
<td>2 arms: • Standard RT and adjuvant ET • Adjuvant ET with no RT</td>
<td>Women aged ≥50 years with luminal A, HR-positive, HER2-negative stage I BC with negative margins and nodal status after BCS; low-risk score on Prosigna assay (≤60)</td>
<td>1167</td>
</tr>
</tbody>
</table>

BC indicates breast cancer; BCS, breast-conserving surgery; ER, estrogen receptor; ET, endocrine therapy; HR, hormone receptor; IBTR, ipsilateral breast tumor recurrence; RT, radiation therapy; RS, recurrence score; WBI, whole breast irradiation.

*Active but no longer recruiting participants.
Use of locoregional recurrence (LRR) and radiosensitivity assays in patients undergoing breast conserving surgery may help to identify patients at sufficiently low risk of LRR to avoid breast radiation therapy.”

In their study population, 10-year rates of LRR were 3.2%, 2.0%, and 10.1% for low, intermediate, and high RS, respectively, which was not statistically significant (P = .17). However, as a continuous variable, RS was a significant predictor of LRR (HR, 2.66, P = .03). Woodward et al recently reported on the retrospective assessment of RS in SWOG 8814, comparing chemo-endocrine versus endocrine therapy in patients with node-negative, hormone receptor-positive breast cancer.49 Estimated 10-year cumulative LRR rates were 9.7% and 16.5%, for low versus intermediate/high RS, respectively (log-rank P = .018). In an analysis of patients who have undergone mastectomy alone, differences in RS remained significant (7.7% low RS vs 16.8% intermediate/high RS; P = .03).

These findings suggest that genomic profiling can significantly predict risk of LRR in patients with node-positive breast cancer, and this association could have clinical implications regarding tailoring regional nodal XRT or PMRT. However, before such an approach becomes accepted clinical practice, validation in prospective clinical trials is needed.

One such trial is CCTG MA.39 that is currently accruing patients through the National Cancer Trials Network (TAILOR RT; NCT03488693). MA.39 includes patients with ER-positive/HER2-negative, node-positive breast cancer and a 21-gene RS of <18. Patients who underwent mastectomy are randomized to chest wall plus regional nodal XRT versus no XRT, whereas patients treated with BCS are randomized to breast plus regional nodal XRT versus breast XRT only. A total of 2140 patients will be included in the study (TABLE).

Adjuvant Breast XRT Following BCS

There have been several attempts to tailor the use of breast XRT following BCS based on primary tumor or patient characteristics.41,42 A previously reported clinical trial using tumor size of <1 cm as a criterion for selecting patients at low risk of in-breast recurrence, who can then be treated with BCS without breast XRT, demonstrated unacceptably high rates of in-breast recurrence when XRT was omitted, even when adjuvant tamoxifen was used.43 Another randomized clinical trial that used age >70 years as a criterion for selecting patients in whom breast XRT could be omitted showed significantly higher rates of in-breast recurrence without breast XRT but no overall survival differences.42

Fitzal et al examined the role of EndoPredict (EP) in predicting LRFS after surgery in 1324 postmenopausal patients with endocrine-responsive breast cancer who were primarily treated with adjuvant endocrine therapy as part of a randomized clinical trial conducted by the Austrian Breast and Colorectal Cancer Study Group (ABCSG 8 trial).44 In addition, 869 women from the ABCSG 8 trial with a low-risk profile (tumor size <3 cm, pTNO and grade 1 and 2) were randomized to breast XRT versus no breast XRT following lumpectomy (ABCSG trial 8a).45 With a median follow-up of 72.3 months, EP was an independent significant predictor of local recurrence (LR) risk.

The risk of LR over a 10-year period was significantly higher in patients with EP high-risk lesions (LRFS, 91%) compared with those who had EP low-risk lesions (LRFS 97.5%; P < .005). On the other hand, EP was not found to be predictive of benefit from breast XRT, as XRT significantly improved LRFS both in the EP low-risk cohort (received XRT: n = 436, 10-year rate of LR, 0.2%; did not receive XRT: n = 63, 10-year rate of LR, 11.1%; P < .005) and in the EP high-risk cohort (received XRT: n = 475; 10-year LRFS, 2.5%; did not receive XRT: n = 75; 10-year LRFS, 12.0%; P < .005).43

Based on these results, there is continuing interest in evaluating whether currently commercially available genomic classifiers can identify subgroups of patients with breast cancer who can be spared breast XRT after BCS. Currently, there are none that can do so. Several prospective trials (both single arm and randomized) are currently under way to address this question in patients with early-stage disease treated with BCS (TABLE).

The LUMINA trial (NCT01791829) is enrolling patients aged >55 years with T1N0 luminal A tumors, onto a single-arm prospective observation trial, with a primary end point to measure the 5-year ipsilateral breast recurrence rate. The IDEA trial (NCT02400190) completed enrollment of patients who were postmenopausal, with T1N0 ER-positive breast cancer and low RS (<18) onto a single-arm prospective observation trial, with a primary end point of 5-year LRR.

The PRECISION trial (NCT02653755) is enrolling women aged >50 years with T1N0 ER-positive breast cancer and a low PAM50 ROR score to a single-arm prospective observation trial, also with a primary end point of 5-year LRR. The EXPERT trial (NCT02889874) is a randomized study of BCS with or without XRT in T1N0 ER-positive breast cancer in women aged >50 years with a PAM50 ROR of less than 60. Until results from these trials become available, BCS plus XRT remains the standard of care for the majority of patients with invasive breast cancer.

Genomic Profiling for Prediction of XRT Benefit

The aforementioned trials were designed to identify patient populations with very low risk of LRR, where addition of chest/breast XRT or regional nodal XRT would not add substantial absolute benefit in local control. Another approach to tailor use of XRT is development of genomic classifiers predictive of XRT benefit, rather than LRR.
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et al. attempted to develop a genomic predictor of XRT benefit in high-risk patients with breast cancer treated with systemic therapy and randomized to PMRT or not. Seven genes were identified, and the derived gene-expression index (DBCG-RT profile), which then divided patients into high-LRR-risk and low-LRR-risk groups. PMRT significantly reduced risk of LRR in high-LRR-risk patients but not in low-LRR-risk patients.

Other investigators have developed genomic predictors of XRT sensitivity using clonogenic survival assays for breast cancer cell lines. Speers et al. developed a 51-gene radiation sensitivity score enriched for genes involved in cell cycle arrest and DNA damage response, whereas Torres Roca et al. developed and validated a radiosensitivity index in established databases of patients treated with BCS plus XRT or mastectomy without XRT.

When combining radiosensitivity index with molecular subtype, patients at the greatest risk of LRR had triple-negative and radiosensitive breast cancer (HR, 0.37; P = .02). Sjostrom et al. utilized fresh frozen tissue from 336 patients undergoing BCS with or without XRT to develop a new radiosensitivity assay with the Nanostring platform, suitable for low-quality RNA analysis. In patients who underwent BCS with a high risk of LRR, investigators identified 3 groups.

In the low-LRR-risk/low-radiosensitivity group, XRT would not reduce risk of LRR. In the second group of patients, XRT was recommended due to high radiosensitivity. In the third group, escalated treatment was recommended, as the patients’ tumors were at high risk for LRR that was not significantly reduced by XRT. More recently, the same group of investigators identified a new 27-gene Adjuvant Radiotherapy Intensification Classifier (ARCTIC) using publicly available gene databases with known outcomes. ARCTIC scores were calculated for patients treated with BCS with or without XRT on the SweBCG91 trial and compared with 8 different genomic signature scores from the aforementioned studies. ARCTIC outperformed the other gene expression scores for predicting elevated risk of LRR as well as benefit from XRT.

**Future Directions**

Although currently available evidence with molecular subtyping/genomic profiling provides great insight on tumor biology and its locoregional behavior, such evidence has not yet translated into meaningful changes in locoregional therapy approaches. In the setting of ER-positive, HER2-negative disease, multiple secondary analyses of randomized studies independently show RS correlates to LRR similar to known prognostic variables, such as lymph vascular space invasion or stage. As such, RS may be incorporated into estimations of LRR risk.

However, care must be taken when omitting XRT off protocol among women with a low RS, given the benefit from breast XRT in reducing in-breast recurrence after BCS and the benefit from PMRT and regional nodal XRT on disease-free survival.

Minimal data are available on the utility of genomic assays for LRR prognosis in the setting of neoadjuvant chemotherapy or with the use of trastuzumab, and this remains a significant gap in knowledge. Development of predictive assays are promising, yet unproven. Studies are needed to prospectively correlate pathological response to XRT with the existing genetic assays for radiosensitivity.

Enrollment in prospective studies such as MA.39 is strongly encouraged, and development of new trials to test the hypothesis that genomic assays can predict XRT benefit are greatly needed.

By individualizing risk of LRR and radiosensitivity with molecular subtyping/genomic classifiers, it is hoped that use and/or extent of adjuvant XRT could be tailored. Studies such as MA.39 will provide information on whether these assays can guide decision making for PMRT in patients with 1 to 3 positive lymph nodes. Use of LRR and radiosensitivity assays in patients undergoing BCS may help to identify patients at sufficiently low risk of LRR to avoid breast XRT.

Tailoring of XRT dose or adding radiosensitizers could be considered to improve outcome in patients with high LRR risk and radiosensitive tumors. Another provocative, yet unaddressed, question is whether the use of genomic assays could identify a population of patients with early-stage, hormone-receptor positive disease with primarily local recurrence risk rather than distant recurrence risk, who could be adequately treated with surgery plus XRT alone, without the need for 5 years of adjuvant endocrine therapy.

**For a full list of references, see the article at OncLive.com/link/7647.**
37th Annual MIAMI BREAST CANCER CONFERENCE®
Miami Beach, Florida
March 5-8, 2020

Conference Highlights

Immunotherapy Comes of Age in Breast Cancer
by BRITTANY LOVELY

BREAST CANCER HAS historically been considered an immunologically cold disease, but recent and emerging data are carving out a space for several immunotherapies in the treatment paradigm. As the understanding of breast cancer biology grows more precise, so has exploration of antitumor immune responses in patient subpopulations, especially in those with triple-negative breast cancer (TNBC).1

“When IL-2 and interferon were being tested for melanoma and renal cell [carcinoma], the word on the street was that your body doesn’t see breast cancer cells as being foreign because you have breast cancer cells floating about anyway,” Hope S. Rugo, MD, FASCO, cochair of the 37th Annual Miami Breast Cancer Conference®, said during a presentation at the meeting that Physicians’ Education Resource®, LLC (PER®) hosted in Miami Beach, Florida.

Such viewpoints started changing with an improved understanding of the biology of breast cancer and its more aggressive subtypes such as TNBC and estrogen receptor-negative/HER2-positive disease, Rugo noted. “What we found in analysis of large trials was evidence of an immune response as well as to some degree in the metastatic setting correlated to better outcome.”

Rugo, a professor in the Department of Medicine and director of Breast Oncology and Clinical Trials Education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, traced the recent progress of immunotherapy trials in breast cancer and identified key focus areas for the future of immune checkpoint inhibition in early-stage disease.

The determination of whether it is possible to improve survival through first improving response to treatment arose from subset analysis and checkpoint inhibitor studies designed to look at responses when patients are treated in the first-line setting.

“Responses in patients [with PD-L1-positive disease] in the first-line setting were closer to 25%, so clearly something different was going on here biologically,” said Rugo. “We understood that tumors become less immune sensitive or immunologically responsive over time, as they garner mutations and have genomic chaos with progression.”

Rugo noted that this led investigators to go back to the immunity cycle and look for areas where augmentation was possible.

IMPASSION130
The phase III IMpassion130 trial (NCT02425891) investigated whether the anti-PD-L1 monoclonal antibody atezolizumab (Tecentriq) in combination with nab-paclitaxel (Abraxane) would confer a consistent survival advantage for patients with PD-L1-positive, treatment-naïve, metastatic TNBC.2

Patients were randomly assigned to receive nab-paclitaxel 100 mg/m² on days 1, 8, and 15 of a 28-day cycle with atezolizumab 840 mg (n = 451) on days 1 and 15 or with placebo (n = 451). Treatment was given until disease progression or unacceptable toxicity. Patients were assessed using the SP142 assay, which measures PD-L1 only in the immune cells surrounding and infiltrating the tumor. The results identified that 41% of the total population was PD-L1-positive (≥1% expression).

In the primary analysis, atezolizumab plus nab-paclitaxel resulted in a statistically significant progression-free survival (PFS) benefit in the intention-to-treat population compared with placebo plus nab-paclitaxel (HR, 0.80; 95% CI, 0.69-0.92; P = .0025) and demonstrated a trend toward improved overall survival (OS; HR, 0.84; 95% CI, 0.69-1.02; P = .0840).2

Among patients with PD-L1-positive tumors, the addition of atezolizumab resulted in clinically meaningful improvements in both PFS (HR, 0.62; 95% CI, 0.49-0.78; P <.001) and OS (HR, 0.62; 95% CI, 0.45-0.86). There was no improvement in the patients with PD-L1-negative disease in PFS (HR, 0.93; 95% CI, 0.77-1.11) or OS (HR, 0.957; 95% CI, 0.798-1.1520).2

The FDA approved the combination in March 2019 based on the primary analysis.
of IMpassion130 results. These showed that atezolizumab/nab-paclitaxel reduced the risk for progression or death by 40% compared with nab-paclitaxel alone in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC.3

In a posthoc analysis presented at the 2019 European Society for Medical Oncology Congress, patients with PD-L1-positive tumors continued to show clinically meaningful improvements with the addition of atezolizumab in both PFS (HR, 0.63; 95% CI, 0.50-0.80) and OS (HR, 0.7162; 95% CI, 0.54-0.93).4 “With longer follow-up the survival improvement in patients who had IC+ disease was 7 months, very impressive,” said Rugo. “It’s the first treatment to improve survival other than chemotherapy for triple-negative, metastatic breast cancer.”

“We know that our cancers respond less and have shorter duration of response as they progress through metastatic disease,” Rugo said. Several studies have demonstrated a reduction in both expression of PD-L1 and tumor-infiltrating lymphocytes (TILs) as tumors progress from early- to late-stage disease. Moving therapy forward may lead to improved survival.

KEYNOTE-522
The KEYNOTE-522 trial (NCT03036488) examined neoadjuvant pembrolizumab (Keytruda) in early TNBC. In findings published in the New England Journal of Medicine, pembrolizumab plus platinum-containing chemotherapy extended the pathological complete response (pCR) rate by 13.6 percentage points (64.8% vs 51.2%) compared with chemotherapy alone.5

Patients were assigned pembrolizumab 200 mg every 3 weeks (n = 784) or placebo (n = 390). All patients received 4 cycles of carboplatin plus paclitaxel followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide. Following surgery, adjuvant pembrolizumab was continued for 9 months for patients who had PD-L1-positive breast cancer, most of whom had triple-negative disease, 52% versus 15% non-triple-negative, there seemed to be a marked improvement in overall survival, really quite dramatic,” Rugo said. “These numbers are small, but it is quite encouraging that there may be a role for maintenance immunotherapy.”

Future directions for the field include looking at novel combination strategies that may offer great promise (TABLE).1 Explorations into benefit for HER2-positive and estrogen receptor–positive disease are also being actively explored. “Immunotherapy is a reality now for breast cancer,” Rugo concluded.

<table>
<thead>
<tr>
<th>TABLE. Ongoing Phase III Studies of Immunotherapy in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial (ClinicalTrials.gov identifier)</strong></td>
</tr>
<tr>
<td><strong>Neoadjuvant/Adjuvant</strong></td>
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<tr>
<td>IMpassion031a (NCT03197935)</td>
</tr>
<tr>
<td>Arm 2: Chemotherapy</td>
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<tr>
<td>KEYNOTE-522a (NCT03036488)</td>
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<td>Arm 2: Chemotherapy</td>
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<tr>
<td><strong>Adjuvant</strong></td>
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<td>ALEXANDRA/IMpassion030a (NCT03498716)</td>
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<td>Arm 2: Chemotherapy</td>
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<td>SWOG S1418/NRG BRR06a (NCT02954874)</td>
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<td>Arm 2: Pembrolizumab</td>
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<td><strong>Metastatic</strong></td>
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<td>KEYNOTE 355a (NCT02819518)</td>
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<tr>
<td>Arm 1: Pembrolizumab + nab-paclitaxel</td>
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<tr>
<td>Arm 2: Pembrolizumab + paclitaxel</td>
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<tr>
<td>Arm 3: Pembrolizumab + gemcitabine/carboplatin</td>
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<tr>
<td>Part 2</td>
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<tr>
<td>Arm 1: Pembrolizumab + chemotherapy</td>
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<td>Arm 2: Chemotherapy</td>
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<td>IMpassion 131a (NCT03125902)</td>
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<td>Arm 2: Paclitaxel</td>
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<td>IMpassion 132a (NCT03371017)</td>
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<tr>
<td>Arm 2: Chemotherapy</td>
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</table>

**REFERENCES**

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Antibody-Drug Conjugates Show Encouraging Activity in TNBC

by HANNAH SLATER

NOVEL ANTIBODY-DRUG CONJUGATES (ADCs) have demonstrated high response rates in patients with heavily pretreated metastatic breast cancer, and ongoing studies targeting actionable cell-surface markers may further expand their clinical utility, according to Aditya Bardia, MD, MPH.

There are several ADCs in development that target cell-surface markers in triple-negative breast cancer (TNBC), namely TROP-2, LIV-1, HER2, and HER3. These ADCs consist of a high-affinity antibody linked with a toxic payload. They bind to the target antigen and are internalized by the cell, where the linker is degraded by the lysosome to release the cytotoxic payload within the cancer cell, causing apoptosis.1

“The question is how can we further improve the response rates,” explained Bardia, director of Precision Medicine at the Center for Breast Cancer and founding director of the Molecular and Precision Medicine Metastatic Breast Cancer Clinic, Massachusetts General Hospital Cancer Center, and assistant professor of medicine, Harvard Medical School. “We saw a response rate of 30% to 40% with these antibody-drug conjugates; can we improve that to 50%, 60%, 70%, 80%, and further improve the outcomes of patients with metastatic breast cancer?”

SACITUZUMAB GOVITECAN
Sacituzumab govitecan targets TROP-2 to release SN-38, the active metabolite of irinotecan. In a phase I/II single-arm open-label study, Bardia, along with other investigators, found that sacituzumab govitecan showed durable objective responses in pretreated patients with metastatic TNBC, with myelotoxicity being the major adverse effect.5

The study included 108 patients with TNBC. Sacituzumab govitecan was administered at 10 mg/kg on days 1 and 8 of each 28-day cycle.2

In results that were published in the New England Journal of Medicine, at a median follow-up of 9.7 months, the objective response rate (ORR) was 33.3% by local assessment (95% CI, 24.6%-43.1%) with a median duration of response (DOR) of 7.7 months (95% CI, 4.9-10.8). The clinical benefit rate (ORR plus stable disease) was 45.4%. By blinded independent central review, the ORR was 34.3% (95% CI, 25.4%-44.0%) and the median DOR was 9.1 months (95% CI, 4.6-11.3).2

The median progression-free survival (PFS) was 5.5 months (95% CI, 4.1-6.3), and the estimated 6-month PFS rate was 41.9%. By 12 months, the PFS rate with sacituzumab govitecan was estimated at 15.1%. The median overall survival (OS) was 13.0 months (95% CI, 11.2-13.7), with an estimated 6-month OS rate of 78.5% and a 12-month estimate of 51.3%.2

Based on these findings, in December 2019 the FDA accepted a biologics license application for sacituzumab govitecan as a treatment for patients with metastatic TNBC who have received at least 2 prior therapies for metastatic disease.6

The phase III ASCENT trial (NCT02574455) is currently exploring sacituzumab govitecan in comparison with treatment of physician choice for patients with metastatic TNBC. The trial, which has fully accrued 529 patients, is expected to report results in 2020, Bardia said. Findings from ASCENT will act as confirmation.3

The efficacy of sacituzumab govitecan will also be evaluated in the phase II NeoSTAR trial (NCT04230109; TABLE). LADIRATUZUMAB VEDOTIN

The ADC ladiratuzumab vedotin (SGN-LIV1A) consists of an anti–LIV-1 monoclonal antibody connected to a monomethyl auristatin E microtubule disrupting agent via a protease-cleavable linker. In phase I findings presented at the 2017 San Antonio Breast Cancer Symposium (SABCS), the ORR was 25% (15 of 60 patients). The median PFS was 11.0 weeks (6.1-12.1) and the median DOR was 13.3 weeks (95% CI, 5.3-19.1).7

The drug is being evaluated in an ongoing phase I study (NCT01969643) in patients with metastatic TNBC who have received ≥2 cytotoxic regimens in the unresectable, locally advanced, or metastatic setting.

At 2019 SABCS, findings were presented from a phase Ib/II study for the combination of ladiratuzumab vedotin with the PD-1 inhibitor pembrolizumab (Keytruda) in patients with locally advanced or metastatic TNBC.5 According to the abstract, among 26 assessable patients, the ORR was 54% with the combination (95% CI, 33.4%-73.4%). Bardia noted that a majority of patients (>90%) treated with the combination experienced some level of decline in tumor size.

The combination of ladiratuzumab vedotin continues to be assessed in a phase I/II study (NCT03310957). The enrollment goal for the study is 97 patients and the estimated completion date is set for May 2020. [FAM-] TRASTUZUMAB DERUXTECAN-NXKI
[Fam-] trastuzumab deruxtecan-nxki (Enhertu), is a novel ADC comprised of 3 components: a humanized anti-HER2

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EXPLORE THE CLINICAL EVIDENCE AND IN-PRACTICE EXPERIENCE AT IBRANCEhcp.com
Gene Profiling Is An Essential Tool for Tailoring Treatment

BY SILAS INMAN

GENE PROFILING ASSAYS can accurately and reproducibly assist decision making for patients with hormone receptor (HR)-positive breast cancer, with the ultimate goal of improving outcomes or avoiding toxicity, according to a presentation at the 37th Annual Miami Breast Cancer Conference® by Debu Tripathy, MD.

“This is an area that touches all of the specialties of breast cancer treatment,” said Tripathy, professor and chair, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center. “In the past 10 to 20 years, we’ve gotten more sophisticated tools, such as gene profiling, to further build out the subsets. We’re focusing on the benefits of chemotherapy, and there are many established prognostic factors that we all commonly use.”

Tailoring therapy can help avoid many of the short- and long-term adverse effects associated with various therapies (TABLE). The main prognostic criteria are tumor size, nodal status, tumor grade, and molecular profile, Tripathy noted. Several predictive factors also exist, which should be considered for each patient. In addition to HR status and HER2 expression levels, tumor grade and gene expression profiles can be used to determine the appropriateness of chemotherapy.

National Comprehensive Cancer Network (NCCN) treatment recommendations provide guidance on the optimal test to use, based on the level of clinical evidence demonstrated in prospective validation, registry, population-based, and clinical trials. Based on findings from the TAILORx (NCT00310180) and MINDACT trials (NCT00433589), respectively, category 1 recommendations are given for Oncotype Dx for node-negative, HR-positive/HER2-negative disease and for MammaPrint for node-negative to 1 to 3 node-positive breast cancer. Of these 2 tests, Oncotype DX is listed as preferred by the guideline and is the only one to provide predictive value.

“There are many other assays that may be performed just as well but they aren’t tied to a randomized clinical trial,” Tripathy said.

TAILORx AND ONCOTYPE DX

The TAILORx trial included more than 10,000 patients with HR-positive, HER2-negative, axillary node-negative breast cancer. Patients were stratified by risk using the Oncotype DX assay, with 9719 having follow-up information available for analysis. Overall, 69% (n = 6711) had an intermediate recurrence score of 11 to 25; 17% (n = 1619) had a score of 10 or lower; and 14% (n = 1389) had a score of 26 or higher.

Those in the low-risk group received endocrine therapy alone whereas patients in the high-risk group were treated with the combination of chemotherapy and endocrine therapy. Patients in the intermediate group were randomized to...
receive either endocrine therapy alone (n = 3399) or chemotherapy plus endocrine therapy (n = 3312). Endocrine therapy most commonly consisted of an aromatase inhibitor for postmenopausal women and tamoxifen alone or with an aromatase inhibitor for premenopausal women. 3

After a median of 7.5 years of follow-up, endocrine therapy alone was noninferior to chemotherapy plus endocrine therapy for invasive disease-free survival (DFS) in the intermediate group (hazard ratio, 1.08; 95% CI, 0.94-1.24; P = .26). Moreover, freedom from recurrence at a distant site was similar between the two groups (hazard ratio, 1.10; 95% CI, 0.85-1.41; P = .48). 3

For patients 50 years or older, there was no additional benefit observed with the addition of chemotherapy for those with risk scores of 0 to 25. In those aged 50 years or younger, however, there was a benefit for adding chemotherapy in the intermediate risk group, although the rationale behind this is still unclear, Tripathy noted.

In this age group in those with a recurrence score of 16 to 20, there was a 1.6 percentage-point difference for 9-year distant recurrence. In the 21 to 25 recurrence score group, 6.5% more patients recurred at 9 years in the endocrine alone arm compared with the chemotherapy plus endocrine arm (86.9% vs 93.4% freedom from recurrence rates). 3

“This might be explained by the fact that women in the younger age group can undergo menopause with chemotherapy, and it might be that benefit and not chemotherapy that is helping them,” said Tripathy. “This is still controversial to see whether we should be using chemotherapy or ovarian suppression instead. This is still a dilemma.”

**TABLE. Short- and Long-Term Effects of Treatment**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Pain, numbness, weakness, decreased mobility, lymphedema</td>
</tr>
<tr>
<td>Radiation</td>
<td>Fatigue, pain, fibrosis, telangiectasia, sarcoma (~0.01% risk)</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Hot flashes, mood changes, vaginal discharge/bleeding/dryness, myalgias, uterine cancer (~1% risk), stroke, thrombosis (~1% risk), osteoporosis/fracture</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Fatigue, nausea, mucositis, infection, cardiomyopathy (1%-2%)</td>
</tr>
<tr>
<td>Biologic</td>
<td>Cardiomyopathy (1%-3%) rhinitis, diarrhea</td>
</tr>
</tbody>
</table>

**MINDACT AND MAMMAPRINT**

Findings from the MINDACT trial 3 helped establish the 70-gene MammaPrint test as a tool for determining whether chemotherapy could be withheld. For this study, patients were stratified based on their clinical and genetic risk. Those with low risk by both measures (n = 2745) did not receive chemotherapy whereas those with high risk for both were treated with chemotherapy (n = 1806). A second group with clinical-low but genetic-high risk (n = 592) or clinical-high but genetic-low risk (n = 1550) were randomized to receive chemotherapy or no chemotherapy. 4

In those with clinical-low/genetic-high risk, the 5-year distant metastasis-free survival (MFS) rate was similar regardless of treatment type, illustrating an ability to avoid chemotherapy. In the chemotherapy arm, the 5-year distant MFS rate was 95.8% compared with 95.0% in the chemotherapy-free arm (hazard ratio, 1.17; 95% CI, 0.59-2.28; P = .6657). For those with clinical-high/genetic-low risk, the 5-year distant MFS was 95.9% in the chemotherapy group versus 94.4% in the chemotherapy-free arm (hazard ratio, 0.78; 95% CI, 0.50-1.21; P = .267). 4

“With this assay, you can really take the higher-risk group, primarily the node-positive ones, and, if they have a low recurrence score, you might

surmise that based on these data they may not benefit from chemotherapy,” said Tripathy. “This is what is reflected in the ASCO [American Society of Clinical Oncology] guidelines.”

The ASCO guidelines 4 note that clinical utility for MammaPrint is only indicated in patients with high clinical risk, for both those with node-negative and node-positive cancers. ASCO also updated its guidelines, following the presentation of the TAILORx results. In these guidelines, chemotherapy is listed as having little to no benefit for those older than 50 years with an Oncotype DX score of less than 26 or those who are 50 years or younger with a score of less than 16. 5

In the NCCN guidelines there are 5 gene tests listed for invasive breast cancer: Oncotype DX, MammaPrint, Breast Cancer Index (BCI), Prosigna PAM50, and EndoPredict. 2 Each of these assays examines different molecular characteristics and varying quantities of genes. The Oncotype DX test uses the expression of 21 genes, MammaPrint examines 70 genes, Prosigna PAM50 is a 50-gene profile, BCI examines 7 key genes and ratios, and EndoPredict is a 12-gene panel. Additional assays continue to be assessed and will be added to the guidelines once they are clinically validated, Tripathy noted.
Study Tests Novel Doublet Designed to Promote Immunity in cSCC

by RACHEL NAROZNIAK, MA

INVESTIGATORS ARE TESTING the hypothesis that administering cetuximab (Erbitux) with an anti–PD-L1 agent will induce immunostimulatory synergy and prolong survival in patients with cutaneous squamous cell carcinoma (cSCC). The phase II Alliance A091802 trial (NCT03944941) will examine the combination of cetuximab and avelumab (Bavencio) versus avelumab monotherapy in approximately 59 patients with advanced cSCC to determine whether the doublet regimen will afford a survival advantage over the single-agent approach.

“The combination has significant potential because in addition to cetuximab’s direct targeting of cSCC, as an IgG1 [immunoglobulin] monoclonal antibody [mAb], it also has the potential to induce antibody-dependent cell-mediated cytotoxicity [ADCC] and subsequent adaptive immunity, with preclinical data suggesting synergy between combination IgG1 monoclonal antibodies and agents that block the PD-1/PD-L1 pathway. Using avelumab is of particular interest because avelumab also has the potential to induce ADCC,” said Dan P. Zandberg, MD, study chair of the Alliance A091802 trial and co-leader of the Head and Neck Cancer Program at the University of Pittsburgh Medical Center Hillman Cancer Center in Pennsylvania.

Avelumab is an anti–PD-L1 IgG1 isotype mAb. IgG1 mAbs are better able to stimulate ADCC, a process of defense in which immune cells identify and eradicate malignant cells, than other isotypes such as IgG2. IgG1 isotype mAbs can activate ADCC in the presence of natural killer cells, which lyse tumor cells, providing additional anticancer activity.1

Combining 2 ADCC-spurring mAbs may lead to the collaborative priming and activation of natural killer cells and thus, greater immunogenesis.1

Patients enrolled in Alliance A091802 will receive a maximum of 24 cycles of avelumab regardless of whether they are randomized to the single-agent control arm or the experimental arm. Those treated with the combination therapy will receive up to 12 cycles of cetuximab with avelumab followed by 12 additional cycles of single-agent avelumab. Patients in the avelumab monotherapy group who experience disease progression will be permitted to cross over to the other cohort to receive the doublet regimen.2

The primary end point is progression-free survival. Secondary end points include the objective response rate and the clinical benefit rate, among others (FIGURE). Of note, Alliance A091802 is open to patients with HIV. “Patients with HIV have traditionally been underrepresented in clinical trials, including in cSCC,” Zandberg said. “This trial includes these patients, which has not been done in prior immunotherapy trials in cSCC and most other solid tumor types.”

EXPANDING THE cSCC ARMAMENTARIUM

Alliance A091802 investigators hope that combination cetuximab and avelumab will broaden the historically limited cSCC tool kit. The 2018 approval of cemiplimab-rwlc (Libtayo) for patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiation was “a great step for this patient population,” said Zandberg.3

Cemiplimab-rwlc is the first and only treatment specifically approved for advanced cSCC and constitutes the standard of care.4 However, a wider portfolio of effective systemic options is needed both for locally advanced cSCC for which there is no surgical intervention and for metastatic disease.

Although cSCC is often effectively managed with radiation or surgical resection when diagnosed at an early stage, each year approximately 40,000 cases of cSCC progress to an advanced stage, when they are more difficult to treat.5 Outcomes among patients with recurrent or metastatic cSCC are typically poor, and an estimated 7000 patients in the United States die each year from cSCC.6 Data from large studies have associated a mortality rate of >70% with metastatic disease.7

cSCC is the second most common type of skin cancer.8 The disease is part of the nonmelanoma skin cancers, which, beyond cSCC, include basal cell carcinoma, Merkel cell carcinoma, and squamous cell carcinoma, according to Omid Hamid, MD, PhD, a dermatologist at the University of Chicago.

FIGURE. AVELUMAB WITH OR WITHOUT CETUXIMAB IN ADVANCED SKIN SQUAMOUS CELL CANCER

PHASE II TRIAL (NCT03944941)

<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provide tissue sample (at least a core needle biopsy) for PD-L1 testing</td>
</tr>
<tr>
<td>• Metastatic or locally advanced unresectable cutaneous squamous cell carcinoma</td>
</tr>
<tr>
<td>• At least 1 lesion that is measurable disease based on RECIST guidelines (version 1.1)</td>
</tr>
<tr>
<td>• ECOG performance status of 0-2</td>
</tr>
<tr>
<td>• Women must submit a urine or serum pregnancy test with a negative result &lt;7 days before registration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control Arm:</th>
<th>Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 29</td>
<td></td>
</tr>
<tr>
<td>End Points:</td>
<td>Primary PFS</td>
</tr>
<tr>
<td>Secondary</td>
<td>ORR, CBR, PFS in patients who progress on avelumab monotherapy, OS, AEs.</td>
</tr>
<tr>
<td>Experimental Arm:</td>
<td>Avelumab + cetuximab</td>
</tr>
</tbody>
</table>

AEs indicates adverse events; CBR, clinical benefit rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
MD, chief of Translational Research and Immunotherapy and director of Melanoma Therapeutics at The Angeles Clinic and Research Institute in Los Angeles, California. Ultraviolet light exposure, whether from the sun or from tanning beds, is known to significantly increases one’s risk for cSCC. Roughly 700,000 new cases are diagnosed each year and cSCC incidence is expected to rise between 2% and 4% each year until 2040.

The development of more effective therapies to treat recurrent and metastatic cSCC will be critical as the malignancy is more widely diagnosed. Patients who experience disease progression on anti–PD-1/PD-L1 regimens constitute a subgroup that is in need of additional treatment options, according to Zandberg.

Because the Alliance A091802 study will permit patients who experience disease progression on avelumab monotherapy to cross over to the cetuximab-avelumab arm, the trial “will evaluate, in an exploratory fashion, [the efficacy of] the combination therapy after failure of [an] anti–PD-1 mAb,” Zandberg said. “This has potential implications for cSCC as well as other malignancies” he added.

The Alliance A091802 study is currently recruiting across more than 300 locations nationwide.

REFERENCES
A FOUNDATION in MM maintenance therapy post auto-HSCT

Lenalidomide (REVLIMID)
- The ONLY preferred National Comprehensive Cancer Network® (NCCN®) Category 1 maintenance therapy post auto-HSCT*
- The ONLY FDA-approved maintenance therapy post auto-HSCT^2
- The #1 prescribed maintenance therapy post auto-HSCT^1

Indications
REVLIMID® (lenalidomide) is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Selected Safety Information: Boxed WARNINGS

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM
See the next spread and Brief Summary for complete Boxed WARNINGS.

EMBRYO-FETAL TOXICITY
- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.
- Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS® program.

HEMATOLOGIC TOXICITY
- REVLIMID can cause significant neutropenia and thrombocytopenia.

VENOUS AND ARTERIAL THROMBOEMBOLISM
- Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving REVLIMID with dexamethasone. Anti-thrombotic prophylaxis is recommended.

CONTRAINDICATIONS
Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. 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 risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

Please see Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
5.7-year median PFS with REVLIMID Maintenance²

3.8 YEAR INCREASE IN MEDIAN PFS VS PLACEBO (UPDATED ANALYSIS: MARCH 2015)†

IFM (Study 2): 1.9-year advantage in median PFS vs placebo‡

Median PFS: 3.9 years with REVLIMID Maintenance (95% CI 3.3, 4.7) (n=307) vs 2.0 years with placebo (95% CI 1.8, 2.3) (n=307) (HR 0.53 [95% CI 0.44, 0.64])

Trial design: CALGB (Study 1) and IFM (Study 2) were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies in newly diagnosed patients 18-70 years (CALGB) and <65 years at diagnosis (IFM) who received auto-HSCT following induction therapy, which must have occurred within 12 months. Patients were randomized 1:1 to receive REVLIMID or placebo maintenance 90-100 days (CALGB) or within 6 months (IFM) post auto-HSCT. Patients were required to achieve at least stable disease following hematologic recovery and CrCl ≥30 mL/min. The primary endpoint for both studies was PFS, based on assessment by investigator, and was defined from randomization to the date of progression or death, whichever occurred first. In both studies, the starting dose of REVLIMID was 10 mg once daily for repeated 28-day cycles. After 3 months, a dose increase to 15 mg once daily occurred in 135 patients (58%) in CALGB, and 185 patients (60%) in IFM. The dose was reduced, interrupted, and/or discontinued as needed to manage toxicity. Patients were treated until disease progression, unacceptable toxicity, or patient withdrawal for any reason. At a preplanned interim analysis, the primary endpoint of PFS was met and both studies were unblinded, and patients continued to be followed as before. Patients in the placebo arm of CALGB were allowed to cross over to receive REVLIMID before disease progression; patients in the IFM study were not recommended to cross over. In IFM, REVLIMID was stopped at the recommendation of the Data Monitoring Committee in January 2011.

*See full NCCN Clinical Practice Guidelines In Oncology* for further detail about recommended therapies.
‡Updated analysis, March 2015. Based on intent-to-treat (ITT) population.
auto-HSCT, autologous hematopoietic stem cell transplantation; CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; IFM, Intergroupe Francophone du Myélome; MM, multiple myeloma; NE, not evaluable; PFS, progression-free survival.
Indications

REVLIMID® (lenalidomide) is indicated as maintenance therapy in adult patients with multiple myeloma (MM) following autologous hematopoietic stem cell transplantation (auto-HSCT).

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Important Safety Information

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM**

**Embryo-Fetal Toxicity**
Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS® program.

Information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

**Hematologic Toxicity (Neutropenia and Thrombocytopenia)**
REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

**Venous and Arterial Thromboembolism**
REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient’s underlying risks.

**CONTRAINDICATIONS**

**Pregnancy:** REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. 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 risk to the fetus.

**Severe Hypersensitivity Reactions:** REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

**WARNINGS AND PRECAUTIONS**

**Embryo-Fetal Toxicity:** See Boxed WARNINGS

- **Females of Reproductive Potential:** See Boxed WARNINGS.
- **Males:** Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.
- **Blood Donation:** Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
Important Safety Information (continued)

REVLIMID REMS® Program: See Boxed WARNINGS: Prescribers and pharmacies must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

Hematologic Toxicity: REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. Patients may require a dose interruption and/or dose reduction. MM: Monitor complete blood counts in patients taking REVLIMID + dexamethasone or REVLIMID as maintenance therapy, every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter.

Venous and Arterial Thromboembolism: See Boxed WARNINGS: Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVLIMID. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended and the regimen should be based on the patient’s underlying risks. Erythropoietin-stimulating agents (ESA) and estrogens may further increase the risk of thrombosis and the use should be based on a benefit-risk decision.

Increased Mortality in Patients With CLL: In a clinical trial in the first-line treatment of patients with CLL, single-agent REVLIMID therapy increased the risk of death as compared to single-agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiovascular failure, occurred more frequently in the REVLIMID arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Second Primary Malignancies (SPM): In clinical trials in patients with MM receiving REVLIMID and in patients with FL or MZL receiving REVLIMID + rituximab therapy, an increase of hematologic plus solid tumor SPM, notably AML, have been observed. In patients with MM, MDS was also observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment.

Increased Mortality With Pembrolizumab: In clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Severe Cutaneous Reactions: Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

Tumor Lysis Syndrome (TLS): Fatal instances of TLS have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

Tumor Flare Reaction (TFR): TFR has occurred during investigational use of REVLIMID for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion.

Impaired Stem Cell Mobilization: A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

Thyroid Disorders: Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before starting REVLIMID treatment and during therapy.

Early Mortality in Patients With MCL: In another MCL study, there was an increase in early deaths (within 20 weeks); 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥10 \times 10^9/L).

Hypersensitivity: Hypersensitivity including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for these reactions.
ADVERSE REACTIONS

Multiple Myeloma

- **Maintenance Therapy Post Auto-HSCT:** The most frequently reported Grade 3 or 4 reactions in ≥20% (REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm.

- The most frequently reported adverse reactions in ≥20% (REVLIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 22%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (4%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (54%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 20%).

DRUG INTERACTIONS

Periodically monitor digoxin plasma levels due to increased Cmax and AUC with concomitant REVLIMID therapy. Patients taking concomitant therapies such as ESAs or estrogen-containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

USE IN SPECIFIC POPULATIONS

- **PREGNANCY:** See Boxed WARNINGS: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

- **LACTATION:** There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.

- **RENAL IMPAIRMENT:** Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis.


Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
REVLIMID® (lenalidomide), Capsules for oral use

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

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM**

Embryo-Fetal Toxicity

Do not use REVLIMID® during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment (see Warnings and Precautions (5.1), and Medication Guide (17)). To avoid embryo-fetal exposure to lenalidomide, REVLIMID® is only available through a restricted distribution program, the REVLIMID REMS® program (5.2). Information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

**Hematologic Toxicity (Neutropenia and Thrombocytopenia)**

REVLIMID® can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors (see Dosage and Administration (2.2)).

**Venous and Arterial Thromboembolism**

REVLIMID® has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with REVLIMID® and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient’s underlying risks (see Warnings and Precautions (5.4)).

## 1 INDICATIONS AND USAGE

### 1.1 Multiple Myeloma

REVLIMID® is indicated as maintenance therapy in adult patients with MM following autologous hematopoetic stem cell transplantation (auto-HSCT).

### 1.2 Renal Function Dose in REVLIMID Maintenance Therapy

Table 3: Dose Adjustments for Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Renal Function (Cockcroft-Gault)</th>
<th>Dose of REVLIMID Maintenance Therapy Following Auto-HSCT for MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clcr 30 to 60 mL/min</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>Clcr below 30 mL/min (not requiring dialysis)</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td>Clcr below 30 mL/min (requiring dialysis)</td>
<td>2.5 mg once daily, On dialysis days, administer the dose following dialysis.</td>
</tr>
</tbody>
</table>

## 4 CONTRAINDICATIONS

### 4.1 Pregnancy

REVLIMID® can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide’s structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant (see Boxed Warning). 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 risk to a fetus (see Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1, 8.3)).

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage for Multiple Myeloma

For patients who are auto-HSCT-eligible, hematopoetic stem cell mobilization should occur within 4 cycles of a REVLIMID-containing therapy (see Warnings and Precautions (5.12)).

**REVLIMID® Maintenance Therapy Following Auto-HSCT**

Following auto-HSCT, initiate REVLIMID® maintenance therapy after adequate hematologic recovery (ANC at least 1000/mcL and/or platelet counts at least 75,000/mcL). The recommended starting dose of REVLIMID® is 10 mg once daily continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity. After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.

**Dose Adjustments for Hematologic Toxicities During MM Treatment**

Dose modification guidelines, as summarized in Table 2 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID®.

### 2.2 Oral Administration

Advise patients to take REVLIMID® orally at about the same time each day, either with or without food. Advise patients to swallow REVLIMID® capsules whole with water and not to open, break, or chew them.

## 3 Absolutes and Neutrophil counts (ANC)

**Neutropenia in MM**

Table 2: Dose Adjustments for Hematologic Toxicities for MM

<table>
<thead>
<tr>
<th>Platelet counts</th>
<th>When Platelets</th>
<th>Recommended Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia in MM</td>
<td>Fall below 30,000/mcL</td>
<td>Interrupt REVLIMID treatment, follow CBC weekly</td>
</tr>
<tr>
<td></td>
<td>Return to at least 30,000/mcL</td>
<td>Resume REVLIMID at next lower dose, continuously for Days 1-28 of repeated 28-day cycle</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>If at the 5 mg daily dose, For a subsequent drop below 30,000/mcL</td>
<td>Interrupt REVLIMID treatment. Do not dose below 5 mg daily for Day 1 to 21 of 28-day cycle</td>
</tr>
<tr>
<td></td>
<td>Return to at least 30,000/mcL</td>
<td>Resume REVLIMID at 5 mg daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle</td>
</tr>
</tbody>
</table>

## 2.5 Dosage Modifications for Non-Hematologic Adverse Reactions

For non-hematologic Grade 3/4 toxicities judged to be related to REVLIMID®, hold treatment and restart at the physician’s discretion at next lower dose level when toxicity has resolved to Grade 2 or below.

2.6 Recommended Dosage for Patients with Renal Impairment

The recommendations for dosing patients with renal impairment are shown in the following table (see Clinical Pharmacology (12.3)).
REVLIMID [lenalidomide], Capsules for oral use

4.2 Severe Hypersensitivity Reactions
REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide [see Warnings and Precautions (5.9, 5.15)].

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
REVLIMID is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death [see Warnings and Precautions (2.1)]. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

REVLIMID is only available through the REVLIMID REMS program [see Warnings and Precautions (5.2)].

Females of Reproductive Potential
Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must either abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Two negative pregnancy tests must be obtained prior to initiating therapy; the first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles [see Use in Specific Populations (8.3)].

Males
Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm [see Use in Specific Populations (8.3)].

Blood Donation
Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

5.2 REVLIMID REMS Program
Because of the embryo-fetal risk [see Warnings and Precautions (5.1)], REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the REVLIMID REMS program.

Required components of the REVLIMID REMS program include the following:
- Prescribers must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.3)] and males must comply with contraception requirements [see Use in Specific Populations (8.3)].
- Pharmacies must be certified with the REVLIMID REMS program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

5.3 Hematologic Toxicity
REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking REVLIMID should have their complete blood counts assessed periodically as described below [see Dosage and Administration (2.1, 2.2, 2.3)].

Monitor complete blood counts (CBC) in patients taking REVLIMID in combination with dexamethasone or as REVLIMID maintenance therapy for MM every 4 weeks for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter. A dose interruption and/or dose reduction may be required [see Dosage and Administration (2.1)]. In the MM maintenance therapy trials, Grade 3 or 4 neutropenia was reported in up to 59% of REVLIMID-treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of REVLIMID-treated patients [see Adverse Reactions (6.1)].

5.4 Venous and Arterial Thromboembolism
Venous thromboembolic events (VTE [DVT and PE]) and arterial thromboembolic events (ATE, myocardial infarction and stroke) are increased in patients treated with REVLIMID.

A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with MM at MM at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (2.6%, 2.0%, and 1.7%) in the RD Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (2.8%, 2.8%, and 3.7%, respectively) [see Boxed Warning and Adverse Reactions (6.1)].

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with MM at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.8%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.5%, and 0.6%, respectively) [see Adverse Reactions (6.1)].

Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g. hyperlipidemia, hypertension, smoking).

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed MM who were treated with REVLIMID and dexamethasone compared to 8.3% thrombosis in patients treated with placebo and dexamethasone. The median time to first thrombotic event was 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.8% in the MPT Arm. The median time to first thrombotic event was 4.3 months in the combined Rd Continuous and Rd18 Arms.

In the AUGMENT trial, the incidence of VTE (including DVT and PE) in FL or MZL patients was 3.4% in the REVLIMID/rituximab arm [see Adverse Reactions (6.1)]. In the AUGMENT trial, the incidence of ATE (including MI) in FL or MZL patients was 0.6% in the REVLIMID/rituximab arm [see Adverse Reactions (6.1)].

Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient’s underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving REVLIMID [see Drug Interactions (7.2)].

5.5 Increased Mortality in Patients with CLL
In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

5.6 Second Primary Malignancies
In clinical trials in patients with MM receiving REVLIMID, an increase of hematologic plus solid tumor second primary malignancies (SPM) notably AML and MDS have been observed. An increase in hematologic SPM including AML and MDS occurred in 5.3% of patients with NDMM receiving REVLIMID in combination with oral melphalan compared with 1.3% of patients receiving melphalan without REVLIMID. The frequency of AML and MDS cases in patients with NDMM treated with REVLIMID in combination with dexamethasone without melphalan was 0.4%.

In patients receiving REVLIMID maintenance therapy following high dose intravenous melphalan and autologous hematopoietic stem cell transplantation (ASCT), hematologic SPM occurred in...
REVLIMID [lenalidomide], Capsules for oral use

7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 12.6% compared to 8.8% in patients receiving placebo with a median follow-up of 91.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.9% of patients receiving REVLIMID maintenance, compared to 2.6% in the placebo alone arm.

In patients with relapsed or refractory MM treated with REVLIMID/ dexamethasone, the incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 23.0% versus 7.3% in the dexamethasone alone arm. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.1% of patients receiving REVLIMID/dexamethasone, compared to 0.6% in the dexamethasone alone arm. Patients who received REVLIMID-containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated in the fixed duration REVLIMID-containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

In the AUGMENT trial with FL or MZL patients receiving REVLIMID/rituximab therapy, hematologic plus solid tumor SPMs, notably AML, have been observed. In the AUGMENT trial, hematologic SPM of AML occurred in 0.6% of patients with FL or MZL receiving REVLIMID/rituximab therapy. The incidence of hematologic plus solid tumor SPMs (excluding nonmelanoma skin cancers) was 1.7% in the REVLIMID/rituximab arm with a median follow-up of 29.8 months (range 0.5 to 51.3 months) [see Adverse Reactions (6.1)]. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

5.7 Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone

In two randomized clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

5.8 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics). 2% of patients treated with REVLIMID and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.9 Severe Cutaneous Reactions

Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myositis, and/or pericarditis. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID discontinuation or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or Dress [see Dosage and Administration (2.5)].

5.10 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Monitor patients at risk closely and take appropriate preventive approaches. In the AUGMENT trial in FL or MZL patients, TLS occurred in 2 patients (1.1%) in the REVLIMID/rituximab arm. TLS occurred in 1 patient (0.5%) in the MAGNIFY trial during the REVLIMID/rituximab induction period; the event was serious, Grade 3 adverse reaction.

5.11 Tumor Flare Reaction

Tumor flare reaction (TFR) has occurred during investigational use of REVLIMID for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of a clinical trial. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare reaction may mimic progression of disease (PD).

In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in Cycle 1 and one patient developed TFR again in Cycle 11. In the AUGMENT trial in FL or MZL patients, TFR was reported in 19/176 (10.8%) of patients in REVLIMID with rituximab arm; one patient in the REVLIMID/rituximab arm experienced a Grade 3 TFR. In the MAGNIFY trial, 9/222 (4.1%) of patients experienced TFR; all reports were Grade 1 or 2 in severity and 1 event was considered as serious.

REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

5.12 Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. In patients who are auto-HSCT candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a REVLIMID-containing treatment or for whom inadequate numbers of CD34+ cells have been collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CXCR4 inhibitor may be considered.

5.13 Thyroid Disorders

Both hypothyroidism and hyperthyroidism have been reported [see Adverse Reactions (6.2)]. Measure thyroid function before start of REVLIMID treatment and during therapy.

5.14 Early Mortality in Patients with MCL

In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the REVLIMID arm versus 7.1% in the control arm. On exploratory multivariate analysis, risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥ 10 X 10^9/L).

5.15 Hypersensitivity

Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for angioedema and anaphylaxis [see Dosage and Administration (2.2)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in detail in other sections of the prescribing information:

• Embryo-Fetal Toxicity [see Boxed Warning, Warnings and Precautions (5.1, 5.2)]
• Hematologic Toxicity [see Boxed Warning, Warnings and Precautions (5.3)]
• Venous and Arterial Thromboembolism [see Boxed Warning, Warnings and Precautions (5.4)]
• Increased Mortality in Patients with CLL [see Warnings and Precautions (5.5)]
• Second Primary Malignancies [see Warnings and Precautions (5.6)]
• Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone [see Warnings and Precautions (5.7)]
• Hepatotoxicity [see Warnings and Precautions (5.8)]
• Severe Cutaneous Reactions Including Hypersensitivity Reactions [see Warnings and Precautions (5.9)]
• Tumor Lysis Syndrome [see Warnings and Precautions (5.10)]
• Tumor Flare Reactions [see Warnings and Precautions (5.11)]
• Impaired Stem Cell Mobilization [see Warnings and Precautions (5.12)]
• Thyroid Disorders [see Warnings and Precautions (5.13)]
• Early Mortality in Patients with MCL [see Warnings and Precautions (5.14)]
• Hypersensitivity [see Warnings and Precautions (5.15)]

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.

Newly Diagnosed MM - REVLIMID Maintenance Therapy Following Auto-HSCT

Data were evaluated from 1018 patients in two randomized trials who received at least one dose of REVLIMID 10 mg daily as maintenance therapy after auto-HSCT until progressive disease or unacceptable toxicity. The mean treatment duration for REVLIMID treatment was 30.3 months for Maintenance Study 1 and 26.1 months for Maintenance Study 2 (overall range across both studies from 0.1 to 108 months). As of the cut-off date of 1 Mar 2015, 48 patients (21%) in the Maintenance
REVLIMID [lenalidomide], Capsules for oral use

Study 1 REVLIMID arm were still on treatment and none of the patients in the Maintenance Study 2 REVLIMID arm were still on treatment at the same cut-off date. The adverse reactions listed from Maintenance Study 1 included events reported post-transplant (completion of high-dose melphalan auto-HSCT), and the maintenance treatment period. In Maintenance Study 2, the adverse reactions were from the maintenance treatment period only. In general, the most frequently reported adverse reactions (more than 20% in the REVLIMID arm) across both studies were neutropenia, thrombocytopenia, leukopenia, anemia, upper respiratory tract infection, bronchitis, nasopharyngitis, cough, gastroenteritis, diarrhoea, rash, fatigue, asthenia, muscle spasm and pyrexia. The most frequently reported Grade 3 or 4 reactions (more than 20% in the REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm.

For REVLIMID, the most common adverse reactions leading to dose interruption were hematologic events (29.7%, data available in Maintenance Study 2 only). The most common adverse reaction leading to dose reduction of REVLIMID were hematologic events (17.7%, data available in Maintenance Study 2 only). The most common adverse reactions leading to discontinuation of REVLIMID were thrombocytopenia (2.7%) in Maintenance Study 1 and neutropenia (2.4%) in Maintenance Study 2.

The frequencies of onset of adverse reactions were generally highest in the first 6 months of treatment and then the frequencies decreased over time or remained stable throughout treatment. Table 5 summarizes the adverse reactions reported for the REVLIMID and placebo maintenance treatment arms.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Maintenance Study 1</th>
<th>Maintenance Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Adverse Reactions a</td>
<td>Grade 3/4 Adverse Reactions b</td>
<td>All Adverse Reactions a</td>
</tr>
<tr>
<td></td>
<td>REVLIMID (N=224) n (%)</td>
<td>REVLIMID (N=224) n (%)</td>
<td>Placebo (N=221) n (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia ≤ %</td>
<td>177 (79)</td>
<td>94 (43)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia ≤ %</td>
<td>162 (72)</td>
<td>101 (46)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia ≤</td>
<td>51 (23)</td>
<td>25 (11)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>47 (21)</td>
<td>27 (12)</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>40 (18)</td>
<td>29 (13)</td>
</tr>
<tr>
<td></td>
<td>Pancytopenia ≤ %</td>
<td>&lt; 1%</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia ≤</td>
<td>39 (17)</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection ≤</td>
<td>60 (27)</td>
<td>35 (16)</td>
</tr>
<tr>
<td></td>
<td>Neutropenic infection</td>
<td>40 (18)</td>
<td>19 (9)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia ≤ c, d</td>
<td>31 (14)</td>
<td>15 (7)</td>
</tr>
<tr>
<td></td>
<td>Bronchitis ≤</td>
<td>10 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis ≤</td>
<td>5 (2)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td></td>
<td>Gastroenteritis ≤</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Rhinitis ≤</td>
<td>&lt; 1%</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Sinusitis ≤</td>
<td>8 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td></td>
<td>Influenza ≤</td>
<td>8 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td></td>
<td>Lung infection ≤</td>
<td>21 (9)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract infection ≤</td>
<td>13 (6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td></td>
<td>Infection ≤</td>
<td>12 (5)</td>
<td>6 (3)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection ≤</td>
<td>9 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract infection bacterial ≤</td>
<td>6 (3)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td></td>
<td>Bacteremia ≤</td>
<td>5 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster ≤</td>
<td>11 (5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td></td>
<td>Sepsis ≤</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>122 (54)</td>
<td>83 (38)</td>
</tr>
<tr>
<td></td>
<td>Nausea ≤</td>
<td>33 (15)</td>
<td>22 (10)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17 (8)</td>
<td>12 (5)</td>
</tr>
<tr>
<td></td>
<td>Constipation ≤</td>
<td>12 (5)</td>
<td>8 (4)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain ≤</td>
<td>8 (4)</td>
<td>7 (3)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper ≤</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 5: All Adverse Reactions in ≥5% and Grade 3/4 Adverse Reactions in ≥1% of Patients with MM in the REVLIMID Vs Placebo Arms*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Maintenance Study 1</th>
<th>Maintenance Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REVLIMID (N=224) n (%)</td>
<td>Placebo (N=221) n (%)</td>
<td>REVLIMID (N=224) n (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0 (0)</td>
<td>&lt;1%</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (23)</td>
<td>30 (14)</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17 (8)</td>
<td>10 (5)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>9 (4)</td>
<td>4 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>71 (32)</td>
<td>48 (22)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>&lt;1%</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>34 (15)</td>
<td>30 (14)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (5)</td>
<td>8 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>16 (7)</td>
<td>3 (1)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>13 (6)</td>
<td>5 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>24 (11)</td>
<td>13 (6)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9 (4)</td>
<td>5 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>16 (7)</td>
<td>15 (7)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>&lt;1%</td>
<td>0 (0)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (3)</td>
<td>8 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>34 (15)</td>
<td>19 (9)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>23 (10)</td>
<td>12 (5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (7)</td>
<td>9 (4)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>8 (4)</td>
<td>&lt;1%</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>5 (2)</td>
<td>0 (0)</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**Note:** Adverse Events (AEs) are coded to Body System/Adverse Reaction using MedDRA v15.1. A subject with multiple occurrences of an adverse reaction is counted only once under the applicable Body System/Adverse Reaction.

- All treatment-emergent AEs in at least 5% of patients in the REVLIMID Maintenance group and at least 2% higher frequency (%) than the Placebo Maintenance group.
- All grade 3 or 4 treatment-emergent AEs in at least 1% of patients in the REVLIMID Maintenance group and at least 1% higher frequency (%) than the Placebo Maintenance group.
- All serious treatment-emergent AEs in at least 1% of patients in the REVLIMID Maintenance group and at least 1% higher frequency (%) than the Placebo Maintenance group.

**Footnotes:**
- a Adverse Reactions for combined ADR terms
- b All adverse reactions under Body System of Infections and Infestation except for rare infections of Public Health interest will be considered listed
- c All treatment-emergent AEs in at least 5% of patients in the REVLIMID Maintenance group and at least 2% higher frequency (%) than the Placebo Maintenance group.
- d Footnote “a” not applicable for either study
- e Footnote “b” not applicable for either study
- f - ADRs where at least one resulted in a fatal outcome
- g - ADRs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
- h - All adverse reactions under Body System of Infections and Infestation except for rare infections of Public Health interest will be considered listed
7.1 Digoxin
When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin Cmax and AUClast were increased by 14%. Periodically monitor digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, during administration of REVLIMID.

7.2 Concomitant Therapies That May Increase the Risk of Thrombosis
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID [see Warnings and Precautions (5.4)].

7.3 Warfarin
Co-administration of multiple doses of REVLIMID (10 mg/day) with a single dose of warfarin (25 mg) had no effect on the pharmacokinetics of lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Risk Summary
Based on the mechanism of action [see Clinical Pharmacology (12.1)] and findings from animal studies [see Data], REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy [see Boxed Warning, Contraindications (4.1), and Use in Specific Populations (5.1)].

REVLIMID is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, microtia, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Antimicrobial, urinary tract, and genital malformations have also been documented and mortality at shortly after birth has been reported in about 40% of infants.

8.2 Lactation
Risk Summary
There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed child, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children from REVLIMID, advise women not to breastfeed during treatment with REVLIMID.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
REVLIMID can cause fetal harm when administered during pregnancy [see Use in Specific Populations (8.1)]. Verify the pregnancy status of females of reproductive potential prior to initiating REVLIMID therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.
**REVLIMID** (lenalidomide), Capsules for oral use

**Contraindications**

- **Lenalidomide** is a member of a class of compounds known as immunomodulatory drugs (IMiDs).

**Indications**

**Multiple Myeloma**

- Lenalidomide in combination with dexamethasone is indicated for the treatment of patients with treatment-naive multiple myeloma.

**Myelodysplastic Syndromes**

- Lenalidomide in combination with dexamethasone is indicated for the treatment of patients with severe (International Prognostic Scoring System [IPSS] Risk > Int-2) myelodysplastic syndromes (MDS).

**Carotid Artery Stenosis**

- Lenalidomide is not indicated for the treatment of carotid artery stenosis.

**Warnings and Precautions**

- **Hematologic Toxicity**
  - Neutropenia, anemia, and thrombocytopenia are common.

- **Venous and Arterial Thromboembolism**
  - Inform patients that they should be monitored for the signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE), including symptoms such as pain in the leg or abdomen, and shortness of breath.

- **Pregnancy and Lactation**
  - Lenalidomide is a pregnancy Category D drug.

- **Second Primary Malignancies**
  - Lenalidomide therapy has been associated with an increased risk of second primary malignancies.

**Precautions**

- **Reproductive Potential**
  - Advise females of reproductive potential to use effective contraception during treatment with lenalidomide and for up to 4 weeks after discontinuing lenalidomide.

- **Laboratory Monitoring**
  - Monitor complete blood cell counts and platelets during treatment with lenalidomide.

**Overdosage**

- **Symptoms**
  - Symptoms of overdose include thrombocytopenia, neutropenia, anemia, and bleeding.

- **Treatment**
  - Supportive care is the primary management of overdose.

**Clinical Pharmacology**

- **Pharmacokinetics**
  - Lenalidomide is rapidly absorbed after oral administration.

- **Drug Interactions**
  - Lenalidomide may increase the risk of bleeding when given concomitantly with other drugs that cause bleeding.

- **Geriatric Use**
  - Elderly patients may have a higher risk of adverse reactions.

**Adverse Reactions**

- **Common**
  - Fatigue, nausea, constipation, and neutropenia.

- **Severe**
  - Thrombocytopenia, neutropenia, anemia, and bleeding.

**Precautions**

- **Breastfeeding**
  - Lenalidomide is excreted in breast milk.

- **Pediatric Use**
  - Lenalidomide is not recommended for use in children.

**Contraindications**

- **Lenalidomide** is contraindicated in patients with severe renal impairment.

**Adverse Events**

- **Hematologic**
  - Neutropenia, anemia, and thrombocytopenia.

- **Cardiopulmonary**
  - Fatigue, dyspnea, and respiratory failure.

**Precautions**

- **Breastfeeding**
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**Contraindications**

- **Lenalidomide** is contraindicated in patients with severe renal impairment.

**Adverse Events**

- **Hematologic**
  - Neutropenia, anemia, and thrombocytopenia.

- **Cardiopulmonary**
  - Fatigue, dyspnea, and respiratory failure.

**Precautions**

- **Breastfeeding**
  - Lenalidomide is excreted in breast milk.
Hepatotoxicity
Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.8)].

Severe Cutaneous Reactions
Inform patients of the potential risk for severe skin reactions such as SJS, TEN, and DRESS and report any signs and symptoms associated with these reactions to their healthcare provider for evaluation. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID [see Warnings and Precautions (5.9)].

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 (5.10)].

Tumor Flare Reaction
Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.11)].

Early Mortality in Patients with MCL
Inform patients with MCL of the potential for early death [see Warnings and Precautions (5.14)].

Hypersensitivity
Inform patients of the potential for severe hypersensitivity reactions such as angioedema and anaphylaxis to REVLIMID. Instruct patients to contact their healthcare provider right away for signs and symptoms of these reactions. Advise patients to seek emergency medical attention for signs or symptoms of severe hypersensitivity reactions [see Warnings and Precautions (5.15)].

Dosing Instructions
Inform patients how to take REVLIMID [see Dosage and Administration (5.2)]
- REVLIMID should be taken once daily at about the same time each day.
- REVLIMID may be taken either with or without food.
- The capsules should not be opened, broken, or chewed. REVLIMID should be swallowed whole with water.
- Instruct patients that if they miss a dose of REVLIMID, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take REVLIMID at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

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Pat. www.celgene.com/therapies
© 2005-2019 Celgene Corporation, All Rights Reserved.
AMONG AN EXPLOSION OF new data, novel therapies, potential biomarker breakthroughs, and improved technology, the field of hepatocellular carcinoma (HCC) is moving toward a more comprehensive, personalized, and optimistic approach in treatment, said Michael R. Charlton, MBBS.

“This is a time to be more optimistic in HCC,” said Charlton. “We are seeing patients who had seemingly hopeless situations now develop into [having] a chronic disease. Our tools are getting better and, in turn, we are getting better at understanding how to use them. We are in as good of spirits as you can be in a difficult situation.”

Charlton is a professor of medicine, director of the Center for Liver Diseases, and codirector of the Transplant Institute at the University of Chicago Medicine. He discussed the evolution of HCC treatment in an interview with OncologyLive® during the 2020 HCC-TAG Conference, held in February in Park City, Utah.

Why is it essential to utilize multidisciplinary care in HCC?

Medicine is [getting] increasingly complicated. I often tell patients that they should think of their healthcare team as an orchestra. There is likely a conductor to that orchestra, but there is also an oncologist, a radiologist, and a surgeon.

The best decisions are made when each of these experts sit around the table thinking about a particular case and deciding what’s the best way forward for a particular patient. It could be a standard of care, surgery, interventional radiology, or something else. It is easily the best way to treat patients.

What is the benefit of early detection of disease for patients with liver cancer?

By the time most people with liver cancer are diagnosed, they have progressed to the point that they are not curable with our current tools. We would love to see more people be screened and surveyed, so they are diagnosed when they have resectable disease or [can be treated] with locoregional therapies.

Sadly, only a minority of patients present with curable disease using our current tools. Hopefully in 5 to 10 years, that group of patients will greatly expand, but as we sit here today, the majority of patients are not curable because they present with late-stage disease.

What does the future of HCC treatment look like to you?

Going forward, we will see an interaction between industries. The National Institute of Health has a lot of resources, but the pharmaceutical industry has more. Investigators have ideas. Of course, patient advocates are an important group. Listening to them all to see the way forward makes the most sense. That collaborative sense of moving the field forward is the best thing about today compared with 1 year ago. Make sure that you are seeing patients in a team setting. You’re so much more likely to get ideas that are best for the patient.

What advice would you give a community oncologist who may not regularly see patients with HCC?

There are updated guidelines to reference, but those guidelines become outdated quickly. Stay abreast through medical meetings, such as the HCC-TAG Conference and ASCO Annual Meeting.

Also, perhaps there is 1 person in [a community practice] who is a champion of HCC. There are so many types of cancer, so no one person can be on top of all of them. Having 1 person who can stay up to the minute with HCC [may be beneficial]. That is how I would approach it if I was a community oncologist.
Deep Data Dive Is Needed for Upfront Therapy Selection in iNHL

by JASON M. BRODERICK

ALTHOUGH THE LONG-TERM overall survival (OS) rate is high for patients with indolent non-Hodgkin lymphoma (iNHL), a careful review of the available data is required to optimize the outcome for each patient.

At the 24th Annual International Congress on Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Myeloma, Sonali M. Smith, MD, detailed the critical clinical trial findings currently informing treatment selection in the frontline iNHL paradigm. Smith is the Elwood V. Jensen Professor in Medicine, interim chief, Section of Hematology/Oncology, and director of the Lymphoma Program at the University of Chicago Medicine in Illinois.

CAN THE “CHEMO-FREE” R2 REGIMEN REPLACE CHEMIOIMMUNOTHERAPY? When therapy is indicated, the frontline armamentarium of iNHL includes chemotherapy, anti-CD20 monoclonal antibodies, and the immunomodulatory drug lenalidomide (Revlimid).

The phase III RELEVANCE trial (NCT01650701) sought to determine whether the “chemotherapy-free” combination of rituximab (Rituxan) and lenalidomide (R2 regimen) could replace the standard chemoimmunotherapy regimen of rituximab plus chemotherapy in the frontline setting for patients with follicular lymphoma (FL).1

The RELEVANCE trial randomized 1030 patients to receive R2 (n = 513) or rituximab/chemotherapy (n = 517), which consisted of R-CHOP (72%), rituximab/bendamustine (23%), and R-CVP (5%). The chemotherapy regimens were given at standard doses. In the R2 arm, lenalidomide was administered at 20 mg/day on days 2 through 22 of a 28-day cycle until complete response/unconfirmed complete response (CR/CRu), then at 10 mg/day. Rituximab was given at 375 mg/m² weekly in cycle 1 and then on day 1 of cycles 2 through 6. It was continued in responders every 8 weeks for 12 cycles.

Baseline characteristics were well-balanced across groups. The median age in both arms was 59 years and two-thirds of patients had ECOG performance status 0. Bulky disease (>7 cm) was found in 42% of those in the R2 group and in 38% of those in the rituximab/chemotherapy group. Follicular Lymphoma International Prognostic Index (FLIPI) score was low (15%), intermediate (36% to 37%), and high (48% to 49%). B symptoms were present for approximately one-quarter of patients.

The study results showed that the combination of rituximab and lenalidomide showed similar efficacy compared with rituximab plus chemotherapy, which failed to satisfy the primary study end points of improved progression-free survival (PFS) and CR rates with the “chemo-free” regimen; however, the R2 regimen demonstrated a more favorable safety profile, making it a potential first-line option.

After 120 weeks, the R2 regimen showed a CR/CRu rate of 48% compared with 53% for rituximab/chemotherapy (P = .13). The objective response rate (ORR) with the R2 regimen was 84% compared with 89% for rituximab/chemotherapy. The 3-year duration of response was 77% with R2 compared with 74% for rituximab/chemotherapy.

At a median follow-up of 37.9 months, PFS was similar in both arms. By independent review, the 3-year PFS rate was 77% with R2 compared with 78% for rituximab/chemotherapy (HR, 1.10; 95% CI, 0.85-1.43; P = .13). The range of grade ≥3 TEAEs was higher in the chemotherapy group (approximately 60% vs 70%). Grade 3/4 infections were twice as likely in the chemotherapy arm (2% vs 5%) and more patients experienced febrile neutropenia in the chemotherapy group (2% vs 7%). The number of patients with febrile neutropenia requiring hospitalization was more than double in the chemotherapy arm (2% vs 5%), and nearly 3 times as many patients received growth factor agents in the chemotherapy group compared with the R2 group (23% vs 68%).

CAN OBINUTUZUMAB REPLACE RITUXIMAB? Recent research in iNHL has addressed whether or not a different anti-CD monoclonal antibody, obinutuzumab (Gazyva), can replace rituximab in the frontline setting.

In November 2017, the FDA approved obinutuzumab in combination with chemotherapy, followed by obinutuzumab alone, for the first-line treatment of patients with advanced FL. The approval was based on findings from the phase III GALLIUM study (NCT01332968).3

The international GALLIUM study included 1401 treatment-naïve patients with iNHL, of whom 1202 had FL. They were randomized to obinutuzumab plus chemotherapy followed by obinutuzumab alone (n = 601), or rituximab plus chemotherapy followed by rituximab alone (n = 601).

The obinutuzumab regimen extended PFS versus the rituximab regimen. The 3-year PFS rate at a median follow-up of 34.5 months (range, 0-54.5) was 80% versus 73.3% with obinutuzumab versus rituximab, respectively (HR, 0.66; 95% CI, 0.51-0.85; P = .001). The ORR was 88.5% versus 86.9%, respectively.

Despite the PFS benefit, there was no
Alectinib Maintains Frontline Efficacy for ALK-Positive NSCLC

by DANIELLE TERNYILA

**UPDATED ANALYSIS OF THE** phase III ALEX trial (NCT02075840) demonstrated the superior efficacy of alectinib (Alecensa), a second-generation ALK inhibitor, versus crizotinib (Xalkori) for the treatment of patients with ALK-positive non-small cell lung cancer (NSCLC), further supporting its use as the preferred first line standard of care.1,2 Alectinib also demonstrated activity in patients with baseline central nervous system (CNS) metastases, further expanding its utility in this patient population.

“There are 2 properties that make this agent unique,” explained Tony S. K. Mok, MD, BMSc, FRCPC, in an interview with OncologyLive®. “First, [alectinib] is able to counteract some of the resistance mutations, and second is the fact that it has high CNS penetration.”

The median progression-free survival (PFS) in the intention-to-treat population was 34.8 months with alectinib, versus 10.9 months in the crizotinib arm. In patients with baseline CNS metastases, the median PFS was 27.7 months versus 7.4 months with alectinib versus crizotinib, and 34.8 months versus 14.7 months in patients without baseline CNS metastases, respectively (HR, 0.35; 95% CI, 0.22-0.56). For patients without baseline CNS metastases, the median PFS was 34.8 months in the alectinib arm versus 14.7 months in the crizotinib arm (HR, 0.47; 95% CI, 0.32-0.71).1

The overall response rate was 82.9% in the alectinib arm, versus 75.5% in the crizotinib arm. Overall survival (OS) data were still not mature at the time of analysis.

The safety of alectinib was also comparable to that of crizotinib. Overall, 44.7% of patients in the alectinib arm and 51.0% in the crizotinib arm experienced grade 3 to 5 adverse events (AEs). There were also fewer fatal AEs in the alectinib arm than the crizotinib arm, 3.9% versus 4.6%, respectively. Fewer AEs related to alectinib led to dose reductions (16.4%) compared with crizotinib (20.5%).

Mok, chairman, Department of Clinical Oncology, Li Shu Fan Professor of Clinical Oncology, The Chinese University of Hong Kong, discussed the data from the ALEX trial and provided an update on the safety of frontline alectinib compared with crizotinib for patients with advanced ALK-positive NSCLC.

**What was the rationale for conducting the ALEX trial?**

The ALEX study is 1 of 3 randomized phase III studies that compare alectinib, which is a second-generation tyrosine kinase inhibitor [TKI] for ALK-positive lung cancer, versus the prior standard of crizotinib. In this study, the aim is to look into the differences of PFS between alectinib and crizotinib.

**What were the PFS data for alectinib compared with crizotinib?**

The initial data that were first published in the New England Journal of Medicine [showed median PFS] was actually not reached in the alectinib arm compared with around 10 months in the crizotinib arm. In this updated data, the median PFS was about 34.8 months versus about 11 months in the crizotinib arm.

**What does the OS look like now?**

The OS of the ALEX study has not yet been reached. However, we managed to look into the 4-year OS rate, meaning the proportion of patients who are still alive after 4 years. It turned out to be 62.5% with alectinib and about 52% for the crizotinib arm.

**What makes alectinib different from earlier generation agents?**

This is a second-generation drug, and there are 2 properties that make this agent unique. First, it is able to counteract some of the resistance mutations, and second is the fact that it has high CNS penetration. In fact, in the first of the randomized studies, we are able to document the so-called CNS progression. In about 1 year, about 40% of patients in the crizotinib arm had progressed in the brain, as compared with only 9.1% of the patients [treated] with alectinib.

**Did alectinib show consistent safety data in this analysis?**

The safety data of alectinib was compared with crizotinib, and there is no exceeding point of concern. Alectinib had some hepatic toxicity. The incidence of cardiotoxicity is low, and also there is some edema, so compared with crizotinib, there is no significant difference.

**What are the clinical implications of these data?**

Based on the original ALEX data published in the New England Journal of Medicine, we basically demonstrated an improvement in the PFS. Over the past 2 years, we have seen that a significant proportion of patients have been using alectinib as a first-line therapy. With the update from the 2019 [European Society of Medical Oncology] ESMO
Annual Meeting, this has confirmed its use [in the frontline space].

**Q** How do brigatinib and ceritinib compare with these data?  
Brigatinib (Alunbrig) had also been compared with crizotinib in a first-line study. It demonstrated a significant improvement in PFS. Certainly, brigatinib is 1 of the choices for first-line therapy. However, we cannot say whether alectinib or brigatinib is better because there is not head-to-head comparison between the 2. Either brigatinib or alectinib can be used as frontline therapy.  
As for ceritinib (Zykadia), it had only been compared to chemotherapy in the ASCEND-4 (NCT01828099) study. In this particular study, the median PFS was about 16 months, or a little bit longer. This is certainly better than chemotherapy. However, the drug is associated with some G1 [gastrointestinal] toxicity. It is an option, but it may not be the most favorable option.

**Q** Where does lorlatinib fit into the treatment landscape?  
Lorlatinib (Lorbrena) is a third-generation TKI against ALK. The drug itself is actually a potent drug, and a randomized phase III study is being conducted now. Hopefully within the next year or 2, we will have that answer. In a sense, lorlatinib has the potential benefit of more potent CNS penetration. However, the most optimal sequence of first- and second-generation agents remains unknown. I am looking forward to the data from this phase III study, and we will adjust at that time.

**Q** How can we anticipate treatment evolving in the ALK space?  
Right now, we have a total of about 5 different agents that have been approved; crizotinib, brigatinib, ceritinib, alectinib, and lorlatinib [are approved] as second-line therapy. In the near future, there is also ensartinib, which is going to come out in a randomized study.

In this space, I think we will still encounter the question of the optimal sequencing, but more importantly, we must address how we deal with resistance. In the future, we will probably have to tailor the treatment paradigm according to the different patterns of resistance.

**REFERENCES**


Regarding upfront rituximab versus obinutuzumab in MZL, Smith shared a subset analysis from the GALLIUM trial of 99 patients with MZL treated with obinutuzumab and 96 patients with MZL treated with rituximab. The results showed that unlike in patients with FL, there was no difference in PFS (P = .49) favoring obinutuzumab. There was also no difference between the 2 arms in response rates, time to new antilymphoma treatment (P = .57), and OS (P = .78).

**KEY TAKEAWAYS**

In her concluding remarks, Smith noted that because the clinical trial data do not yield definitive answers, and because not all iNHLs are the same, the approach to upfront treatment—both induction and maintenance—will vary from patient to patient. She stressed that it is essential to have a discussion with patients regarding their personal preferences. Although it is not yet available, a personalized approach based on individual risk assessment and predictive markers will be the future of treatment selection in this setting, Smith said.

For a full list of references, see the article at OncLive.com/link/7460.
Clinical Perspectives | GYNECOLOGIC MALIGNANCIES

Palliative Care Study Suggests Benefits for Patients With Cervical Cancer

by DANIELLE TERNYILA

PATIENTS WITH ADVANCED-STAGE cervical cancer who received palliative care consultations underwent the same level of treatment but had shorter, less acute, and fewer hospital stays than their counterparts who were not given such referrals, according to retrospective study findings.

A window into the impact of palliative care for this patient population emerged from results of a study involving 153 patients who died of cervical cancer after being diagnosed with the disease from January 2000 through mid-February 2017 and undergoing treatment at Massachusetts General Hospital or Brigham and Women’s Hospital, both in Boston.

A palliative care consultation was significantly associated with a referral to hospice care (P < .001) and death in hospice (P < .001) but fewer measures of aggressive care, according to Alexandra S. Bercow, MD, who presented the findings during the 2020 Society of Gynecologic Oncology Winter Meeting.

In an interview, with OncologyLive®, Bercow, a clinical fellow in obstetrics, gynecology, and reproductive biology at the 2 institutions, discussed the implications of this research.

Q How do outcomes differ by stage in cervical cancer?
The prognosis for patients with cervical cancer varies widely across cervical cancer stages. Patients with stage I have very good prognoses, and oftentimes, they are cured with no recurrence. However, patients diagnosed with advanced disease, such as stage III or IV, carry a 5-year survival rate of only 17%.

Q What are the challenges of treating patients with advanced disease?
The mainstay of treatment for advanced cervical cancer is chemoradiation. Unfortunately, chemoradiation carries high morbidity. It often leads to a high symptom profile and a low quality of life. There are different immunotherapies that may be improving the recurrence rate and remission rate for patients with advanced-stage cervical cancer. There are also many new drugs that people are looking at, such as the immune checkpoint inhibitors.

Q What was the rationale for evaluating palliative care in this population?
There have been many studies on palliative care within gynecologic malignancies, but there haven’t been robust studies looking at palliative care specifically for patients with cervical cancer. Often, it is either just looked at in ovarian cancer or endometrial cancer or gynecologic malignancies in general with a very low proportion of patients with cervical cancer.

In addition, patients with cervical cancer carry a vastly different profile than both ovarian and endometrial cancers. These patients are younger, often from a minority background, have a lower socioeconomic status, lower healthcare literacy, and therefore, have poorer access to healthcare. We hypothesized their uptake in palliative care may be different from their ovarian and endometrial counterparts, given their vastly different end-of-life needs.

Q How did you study this question?
We did a retrospective study, which examined patients who died from cervical cancer at our 2 institutions between 2000 and 2017. We looked through their charts to figure out whether they had been referred to palliative care and then what type of palliative care consultation they had—palliative versus outpatient.

Q What were the findings from this study?
We found several things. The first is that in our 2 groups, patients who did receive a palliative care consult and those who did not were slightly different in age. The women who were referred to palliative care were significantly younger with a median age of 49 compared with 57.5. There was a 47% palliative care referral rate, which is low when you think about the fact that all of these women had died from the disease and likely would have needed palliative care the most.

Q What was the rationale for evaluating palliative care in this population?

We also learned there were more inpatient consultations than outpatient consultations. We found palliative care was significantly associated with a hospice referral and death in hospice. In addition, we discovered that patients who had a palliative care consult spent more time in hospice—21 days—than those who did not have a palliative care consult—12 days.

Finally, we looked at measures of aggressive care that are recommended by the National Quality Forum. We found that palliative care consults were associated with the following: fewer ICU [intensive care unit] admissions; fewer emergency department visits; shorter and less frequent hospitalizations; a decreased death rate in the acute care setting; a decrease in the death rate on the inpatient floor, the ICU, or the emergency department; as well as an increased rate of co-discussion with the primary providers within the patient’s last 30 days of life.

We also found that the 2 groups received the same amount of treatment at the end of life, the same amount of chemotherapy and radiation for the last 30 days of life, and the same amount of invasive procedures in the last 3 months of life. Importantly, that did not lead to increased time spent in the hospital. The patients still spent less time in the hospital, which we think is valuable to quality of life and overall end-of-life care.

Q What is the take-home message?
Of course, it is important to think about the individual patient. Studies have shown time and time again that the earlier we can integrate palliative care into our conversations with our patients and into our treatment, the less resistant they will be, but it may also improve their symptom control. As gynecologic oncologists, we have very limited time to spend with our patients, unfortunately, between operating on them, giving them chemotherapy, and having follow-up visits. We might not always have time to treat every single one of their symptoms as well as we would like to. Incorporating palliative care would create a multidisciplinary picture that allows us to care for our patients more as a whole.
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COMMUNITY ONCOLOGY PRACTICES are experiencing the vast and sudden impact of coronavirus disease 2019 (COVID-19). The pandemic is expected to have a lasting effect as practices begin to implement rapid changes to ensure the protection of their staff and patients, while continuing to find ways to deliver the best care.

“Cancer doesn’t wait for COVID, and we have to treat our patients and serve the community by keeping patients [with cancer] out of the already crowded emergency [departments],” Barbara L. McAneny, MD, managing partner, New Mexico Oncology Hematology Consultants in Albuquerque, New Mexico, said in an interview with OncologyLive®. “We are trying to balance protecting the staff and the patients, who are already immune suppressed, with continuing to take care of patients with cancer.”

Although the risk of COVID-19 to patients with cancer is unknown, the potential threat of COVID-19 to immunocompromised patients as a result of their disease or the treatment is thought to be significant. Early published reports from China on the outcomes of patients with cancer infected with COVID-19 indicated 3.5 times higher risk of mechanical ventilation, intensive care unit (ICU) admission, or death compared with patients without cancer.1

Adults and children with serious chronic health conditions, including cancer, are at a higher risk of developing more serious complications from contagious illnesses, such as COVID-19. Chemotherapy can weaken the immune system and increase the risk of any infection, including with SARS-CoV-2, the virus that causes COVID-19.2

A report on COVID-19 in those with cancer and those without cancer found that 39% of patients with cancer (7/18) had a higher risk of severe adverse events (AEs), a composite end point defined as the percentage of patients being admitted to the ICU who require invasive ventilation or who die, compared with 8% (127/1572) of patients without cancer (P = .0003).3 Patients who underwent chemotherapy or surgery in the past month had a numerically higher risk (75%; 3/4 patients) of clinically severe AEs than those who did not receive chemotherapy or surgery (43%; 6/14 patients). Cancer history represented the highest risk for severe AEs. Additionally, age was the only risk factor for severe AEs (OR, 1.43; 95% CI, 0.97-2.12; P = .072).

McAneny said there is likely to be a longer-term impact of the COVID-19 pandemic on patients and practices. “There could be a delay in cancer diagnoses. People won’t be going to the doctor for check-ups, they won’t be getting their mammograms, and they won’t be getting their colonoscopies, which means cancers have time to grow. And then when this lifts, people will be rushing to their doctors and then we’ll see a big uptick in the volume of patients, and we’ll have to figure out how to manage staff and physicians.”

CHANGING OFFICE OPERATIONS
The oncology practices OncologyLive® spoke with have put in place new procedures to minimize risk to patients, including cleaning and sanitizing exam rooms between patients, wearing personal protective equipment when seeing patients, limiting nonpatient visitors who can come to the office, and taking temperatures of patients to screen for possible infection, including COVID-19.

Additionally, clinics are practicing social distancing, which can be difficult when treating patients with cancer. “This is a clinic where the staff hug patients, take their hands, and touch them to provide support, and we’re not doing those [things],” McAneny said. “It feels cold and disconnected. We’ve gotten to be masters at the elbow bump and saying this is a virtual hug.”

However, even with the best protocols in place, managing exposure is a constant challenge. For example, 1 practice that is a member of the Community Oncology Alliance had to close one of its offices for 14 days and quarantine all staff and providers at that site.
This practice, which wanted to remain anonymous, had to call all patients to let them know of the exposure and reschedule appointments to another site.

Some practices are struggling with supply shortages. At New Mexico Oncology Hematology Consultants, some supplies are on back order, McAneny said. “We’re limited in the number of masks we can buy, and some things are on back order. We’re very worried about having enough supplies as this goes forward. We’re also stocking up on chemotherapy because we don’t know if we’ll be getting those drugs over the next few months. We have the expense of purchasing drugs that we don’t know whether we’ll be using or not.”

The FDA’s Oncology Center of Excellence (OCE) is working to anticipate and prevent drug shortages. OCE is in regular contact with the FDA’s drug shortages staff within the Center for Drug Evaluation and Research (CDER). The FDA is proactively monitoring the supply chain, and OCE is working closely with CDER to prevent or mitigate shortages of oncology drugs that are critical to the treatment of patients with cancer. Shortage notifications and updates may be reported to the FDA at drugshortages@fda.hhs.gov.

Some practices are struggling with staffing issues as well. Staff with children were affected when school and daycare facilities closed, said Kathy W. Oubre, MS, chief operations officer, Pontchartrain Cancer Center in Covington, Louisiana, in an interview. “One of the things we did was give people an additional 3 days of paid time off because we anticipated this was going to be a problem.”

Oubre says staff stress and anxiety have also increased. “I was on a call with some of my peers across the country, and this [concern] was echoed by others; we were talking about what we can do for our staff. We are bringing in smoothies as a snack and ordering lunch for the offices once or twice per week. I am also encouraging people to walk at lunch. We owe it to our staff to make sure they will be OK, because if our staff burn out, it won’t help us. It’s our responsibility to make sure we take care of them also.”

### ADJUSTING PATIENT TREATMENTS
Mark K. Kyei, MD, an oncologist with the Cleveland Clinic Independence Family Health Center, in Independence, Ohio, has also put measures in place to protect staff and patients. “Patients [with cancer] who are actively being treated and who are on lifesaving treatments are still being treated. But we are taking extra [precautionary] measures. We are conducting virtual visits and phone visits for benign hematology cases and for patients under active surveillance. Physicians and nurses are putting on necessary personal protective gear, such as face masks. We are cleaning down rooms with appropriate disinfectants,” he said in an interview.

Kyei predicts his practice will be impacted by COVID-19 for the long term. “We don’t know how long this pandemic is going to last. If it is several months, it is going to have a ripple effect. Down the line, once everything settles down, getting back up to speed with our old practices won’t be something that happens overnight. It’s going to be a slow process, and it is going to take a year or two to get back to normal. The economy is being impacted by this and it will have a trickle-down effect on healthcare. If this pandemic continues beyond 6 months, it will take us years to recover.”

In the meantime, cancer organizations are providing resources and advice during the coronavirus pandemic. Organizations such as the American Society of Clinical Oncology (ASCO) are encouraging anyone caring for patients with cancer to follow the existing Centers for Disease Control and Prevention (CDC) guidance when possible. ASCO recommends following local and state public health directives and guidance on who should be tested and how the tests should be conducted, and suggests

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**TABLE. SUMMARY OF MEDICARE TELEMEDICINE SERVICES**

<table>
<thead>
<tr>
<th>Type of Service</th>
<th>What Is the Service</th>
<th>HCPCS/CPT Code</th>
<th>Patient Relationship With Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare telehealth visits</td>
<td>A visit with a provider that uses telecommunications systems between a provider and a patient</td>
<td>Common telehealth services include: 99201-99215 (office or other outpatient visits) G0425-G0427 (telehealth consultations, emergency department or initial inpatient) G0406-G0408 (follow-up inpatient telehealth consultations furnished to beneficiaries in hospitals or SNF)</td>
<td>For new* or established patients</td>
</tr>
<tr>
<td>Virtual check-in</td>
<td>A brief (5-10 minutes) check-in with a practitioner via telephone or other telecommunications device to decide whether an office visit or other service is needed; a remote evaluation of recorded video and/or images submitted by an established patient</td>
<td>HCPCS code G2012 HCPCS code G2010</td>
<td>For established patients</td>
</tr>
<tr>
<td>E-visits</td>
<td>A communication between a patient and their provider through an online patient portal</td>
<td>99421 99422 99423 G2061 G2062 G2063</td>
<td>For established patients</td>
</tr>
</tbody>
</table>

CPT indicates common procedural technology; HCPCS, healthcare common procedure coding system; HHS, US Department of Health & Human Services; SNF, skilled nursing facility.

*To the extent the 1135 waiver requires an established relationship, HHS will not conduct audits to ensure that a prior relationship existed for claims submitted during this public health emergency.
that physicians follow the CDC’s guidance to reschedule elective surgeries at in-patient facilities whenever possible.

While there is no specific evidence or published guidance to support delaying or interrupting adjuvant chemotherapy, ASCO said clinical decisions should be individualized to consider factors such as the risk of cancer recurrence if adjuvant chemotherapy is delayed, modified, or interrupted; the number of cycles of adjuvant chemotherapy already completed; and the patient’s tolerance of treatment.

In a soon-to-be-released paper, experts from the Seattle Cancer Care Alliance—of the National Comprehensive Cancer Network—are sharing insights and advice with oncology care physicians on how to provide optimal cancer care during the COVID-19 pandemic.1 The authors highlight the importance of organizational structure, preparation, agility, and a shared vision for continuing to provide cancer treatment to patients in the face of uncertainty and rapid change.

MANAGING CARE WITH TELEHEALTH

One way that practices are managing patient care during the COVID-19 pandemic is through telehealth. Effective March 6, the Centers for Medicare & Medicaid Services (CMS) broadened access to telehealth so that beneficiaries can receive a wider range of services from their doctors.2 CMS expanded this benefit on a temporary and emergency basis under the 1135 waiver authority and Coronavirus Preparedness and Response Supplemental Appropriations Act. Under this new waiver, Medicare will pay for office, hospital, and other visits furnished via telehealth across the country, including in the patient’s home (TABLE).3

Originally, CMS designed telemedicine to be a rural healthcare option, Oubre said. “It required the patient to be in a clinic using a secure computer. This waiver allows patients to be in their homes. The waiver also allows telehealth visits to be done on cell phones through Skype or FaceTime. This waiver has taken away some of the barriers to telehealth.”

Oubre pointed out that verbal consent needs to be documented with each telehealth visit. Additionally, she cautioned that this waiver is temporary, and CMS has already said that once the emergency is over the telehealth policy goes back to its original form. “Practices also need to check with their malpractice insurers to make sure they cover telehealth,” she said. “Additionally, telehealth is only billable for the state the practitioner practices in. If you have a clinic near the border of another state, you may not be covered for a telehealth visit in that other state. Everyone needs to be very cautious, do their due diligence, and make sure services will be covered by the insurance companies they work with.”

REFERENCES
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Controversy Surrounds Treatment of High-Risk Smoldering Myeloma

by SHARMILAN THANENDRARAJAN, MD

MULTIPLE MYELOMA IS A highly refractory and relapsing type of hematological malignancy in which cure is achievable only in a select patient population with low-risk disease. Predictive cure models used at University of Arkansas for Medical Sciences reveal that 6% to 31% of patients with multiple myeloma have the potential to achieve cure with the more intense Total Therapy treatment regimen. However, a vast majority of patients remain incurable and reveal refractory and relapsing course of disease over time.

Recently, suggestions were made to start systemic treatment in earlier stages of disease, when patients are clinically asymptomatic and not yet transformed to multiple myeloma. Smoldering myeloma, a stage preceding multiple myeloma, is defined by the presence of serum and/or urine monoclonal protein and/or clonal plasma cell infiltration between 10% and 60% in the absence of end-organ damage, such as anemia, hypercalcemia, renal insufficiency, and bone lesion. Until now, it was a general dogma among myeloma experts to employ a watch-and-wait strategy at this stage.

REFINING OUR UNDERSTANDING OF SMOLDERING MYELOMA

Over the past couple of years, it was revealed that smoldering myeloma behaves in different ways with various dynamics of progression to multiple myeloma. Some patients transform within a short period, whereas others remain in a smoldering stage over years or decades without requiring treatment. In particular, patients with ≥10% plasma cell in the bone marrow and serum M-protein of ≥3 g/dL have a significantly higher transformation rate, indicating high-risk smoldering myeloma. The transformation rate from smoldering to multiple myeloma is approximately 10% per year for the first 5 years, 3% per year for years 5 to 10, and 1% per year for the following 10 years.

Our myeloma group has published a 4-gene signature that can reliably distinguish between high-risk and low-risk smoldering myeloma, revealing a 2-year transformation rate of 5% in patients with low-risk disease versus 86% in those with high-risk disease.

Other risk factors identified for high-risk smoldering myeloma include the presence of immunoglobulin A subtype, immunoparesis with reduction of 2 uninvolved immunoglobulin subtypes, progressive increase of M-protein levels by 25% on 2 successive evaluations within a 6-month period, clonal plasma cell involvement in the bone marrow between 50% and 60%, increased circulating plasma cells in peripheral blood, magnetic resonance imaging-defined diffusion abnormalities or 1 focal lesion, and presence of a focal lesion with increased uptake without underlying osteolytic bone destruction in the positron emission tomography-computed tomography. Moreover, cytogenetic abnormalities such as t(4;14), deletion 17p, and gain of 1q are indicative of high-risk smoldering myeloma.

TREATMENT APPROACHES

Several studies have been conducted to treat patients with high-risk smoldering myeloma with either a doublet or triplet regimen in a more conservative approach. Data from the QUIREDEX study (NCT00480363), conducted by the Spanish Myeloma Group, demonstrated that patients treated with lenalidomide (Revlimid) and dexamethasone had a significantly lower transformation rate from smoldering to multiple myeloma compared with the observation group (39% vs 86%, respectively). In addition, the time to progression to myeloma was significantly delayed in the treatment arm compared with the observation arm at 47 months versus 23 months, respectively.

Lonial et al published similar results in a randomized clinical trial, in which patients with intermediate- or high-risk smoldering myeloma receiving lenalidomide as a single agent were compared with an observational group. After a 35-month follow-up, the progression free survival (PFS) was significantly longer with lenalidomide compared with the observational arm (HR, 0.28; 95% CI, 0.12-0.62; P = .002). In the treatment and observational groups, the 1-year, 2-year, and 3-year PFS rates were 98%, 93%, and 91% compared with 89%, 76%, and 66%, respectively.

A triplet regimen consisting of carfilzomib (Kyprolis), lenalidomide, and dexamethasone also demonstrated significant efficacy in patients with high-risk smoldering myeloma, leading to minimal residual disease (MRD) negativity in 92% (11 of 12) of patients.

So far, conservative treatment concepts using doublet and triplet regimens have been introduced only for patients with high-risk smoldering myeloma. These regimens have demonstrated significant improvements in PFS, delay in transition to multiple myeloma, and achievement of MRD negativity.
FUTURE DIRECTIONS
Several unanswered questions remain for this patient population. For example, which dose and combination should be used to treat patients with high-risk smoldering myeloma and for how long? Additionally, how should a relapse, refractoriness, and progression of high-risk smoldering myeloma be approached? A cure concept has not yet been established for asymptomatic and untreated patients with high-risk smoldering myeloma, and debate needs to be initiated surrounding how these patients can be treated sustainably while also taking into account their age, comorbidities, fitness, personal preference, and adverse events of the therapeutic agents.

A long-term approach and perspective are lacking with the current available clinical trials for patients with high-risk smoldering myeloma. In particular, for patients who are younger and those considered fit without comorbidities, more intensive treatment concepts with up-front stem cell collection and high-dose chemotherapy with autologous stem cell transplantation need to be discussed. Additionally, further clinical trials have to be established to underline the importance of a cure concept from the beginning.

REFERENCES
CML Research Aims to Improve a “Magic Bullet”

by JANE DE LARTIGUE, PHD

APPROVAL OF IMATINIB (Gleevec) almost 20 years ago heralded the arrival of the targeted therapy era in oncology and thrust the ABL1 kinase into the limelight. A fusion involving the ABL1 gene is present in the vast majority of patients with chronic myeloid leukemia (CML), and aberrant ABL1 kinase activity is the central oncogenic driver in this cancer type.2

An inhibitor of the BCR-ABL1 protein, imatinib shaped a new standard of care for patients with CML. To address its limitations, including drug resistance, second and third generations of inhibitors have been developed. These agents have ultimately demonstrated superior efficacy to imatinib and expanded the frontline treatment arsenal for CML.3-5

Credited with transforming patients’ prognosis,6 BCR-ABL1 inhibitors do not yet offer a traditional “cure,” but they do promise long-term and, in some cases, potentially treatment-free disease control.7-9

The most recently approved BCR-ABL1 inhibitor, ponatinib (Iclusig), reflects efforts to specifically address the highly resistant BCR-ABL1 T315I mutation that drives resistance to all other BCR-ABL1 inhibitors.10

However, ponatinib is far from the final chapter; the story continues to evolve, with several new inhibitors in clinical development.

Novartis’ asciminib (ABL001) stands out for its novel mechanism of action; it is a first-in-class allosteric inhibitor that selectively targets ABL kinases.11 This mechanism contrasts with the currently approved agents, which inhibit BCR-ABL1 activity by competing with adenosine triphosphate (ATP) for binding to the ATP binding site on the kinase. Asciminib has demonstrated promise as both monotherapy and in combination with traditional inhibitors, indicating that the best may be yet to come in leukemia treatment.11-14

A CANCER ENABLER

ABL1 and the highly homologous protein ABL2 (also known as ABL-related gene [ARG]) are nonreceptor tyrosine kinases (NRTKs), a subgroup of the tyrosine kinase enzyme family that lacks the receptorlike features of extracellular ligand-binding and transmembrane domains.15

NRTKs tend to be found in the cytoplasm, although they can be anchored to the membrane.15 ABL1 contains a DNA-binding domain, nuclear localization signal, and nuclear export signal, which allow it to localize to both the nucleus and the cytoplasm. ABL2 lacks these domains and is exclusively cytoplasmic.

Both proteins contain SRC homology domains (SH1, SH2, and SH3), an N-terminal cap region (which can be modified by myristoylation and plays a critical regulatory role in ABL kinase activity), F-actin-binding domains, and proline-rich sequences (the latter mediating interactions with other proteins).2,16

In normal cells, the ABL kinases are activated by a wide range of stimuli and function in diverse cellular processes, including many of the hallmarks of cancer, such as proliferation and migration, in addition to cytoskeletal reorganization, adhesion, and beyond.16

The ABL1 gene was first described in 1970 as the normal cellular counterpart of a virally encoded gene found in a mouse leukemia virus that could transform normal mouse lymphocytes and fibroblasts. The viral protein was shown to have tyrosine kinase activity.16,17

About 10 years earlier, investigators had discovered an unusual chromosome in the leukocytes of patients with CML, dubbed the Philadelphia chromosome after the city in which it was first described. Through a series of seminal studies, it was shown that the Philadelphia chromosome is the result of a chromosomal translocation involving chromosomes 22 and 9, the latter containing the human ABL1 gene (FIGURE 1).17,18

This chromosomal translocation generates a gene fusion, in which the ABL1 gene is fused in frame with a second gene known as breakpoint cluster region...
The fusion results in constitutive activation of ABL1 kinase activity, which drives development of leukemia by promoting uncontrolled proliferation of undifferentiated immune precursor cells.\(^4,17,18\)

The Philadelphia chromosome has been shown to be present in leukemia cells in more than 95% of CML cases and has been identified in a significant proportion of patients with acute lymphoblastic leukemia (ALL). The specific transcript involved in B-cell ALL is slightly different as a result of different breakpoints within the BCR gene, and it encodes a lower-molecular-weight protein referred to as p190BCR-ABL1; in CML, it is p210BCR-ABL1.\(^18\)

Oncogenic fusions involving both ABL1 and ABL2 have been identified in other forms of leukemia, such as T-cell ALL and acute myeloid leukemia, but have not been explored to the same degree.\(^16,19\) In the past decade, a potential role of ABL kinases in solid tumors also began to be appreciated. The mechanism of ABL activation is different in solid tumors; increased gene and protein expression and, more rarely, somatic mutations, rather than gene fusions, have been observed across a range of solid tumors, more commonly involving ABL2 than ABL.\(^20\)

**POSTER CHILD FOR PRECISION MEDICINE**

The significance of the BCR-ABL fusion in CML prompted a search for small molecules that could block its oncogenic kinase activity. Imatinib was the first tyrosine kinase inhibitor approved by the FDA for the treatment of cancer, earning it the cover of *Time* magazine, which described it as a “magic bullet.”\(^21\)

Imatinib also inhibits c-KIT and platelet-derived growth factor receptor-α kinases. It was shown to be safe and effective across all phases of CML and was first approved for the treatment of Philadelphia chromosome-positive (Ph+) CML for patients resistant or intolerant to interferon alfa, the standard of care at the time.\(^1\) The following year, imatinib was approved for the treatment of all patients with newly diagnosed CML after it demonstrated superior efficacy in the phase III IRIS trial (NCT00006343).\(^22\)

Later, imatinib was approved for patients with Ph+ ALL, in both the relapsed/refractory and frontline settings, with the latter in combination with chemotherapy and only in pediatric patients.\(^23\)

Although the development of imatinib was undoubtedly a significant advancement, many patients are either intolerant or experience progression due to resistance. Numerous mechanisms of resistance have been uncovered, including those involving secondary BCR-ABL1 mutations that block imatinib binding or render it ineffective and those that are BCR-ABL1 independent, such as reduced drug uptake or increased drug efflux.\(^4\)

The second-generation BCR-ABL1 inhibitors, dasatinib (Sprycel), nilotinib (Tasigna), and bosutinib (Bosulif), were designed to address these shortcomings. Like imatinib, they are ATP-competitive inhibitors, and each targets other kinases in addition to ABL, which leads to unique toxicity profiles.\(^4,18\)

All 3 drugs were initially approved in the second-line setting after failure of imatinib and have subsequently been approved in patients with newly diagnosed CML following clinical trials demonstrating faster and deeper treatment responses, although none has been shown to improve overall survival (OS) to date.\(^24-26\)

Although these drugs can successfully overcome many mechanisms of resistance to imatinib, they are all ineffective in the face of the so-called gatekeeper mutation, T315I, a single-amino acid change that alters the accessibility of the ATP-binding pocket of BCR-ABL.\(^2\) The only available third-generation drug, ponatinib, was designed to specifically inhibit this mutation and was approved for the treatment of patients with T315I-positive CML and ALL and for patients with these cancers for whom no other therapy is indicated.\(^27\)

Ponatinib is currently approved only in the second-line setting in both disease indications. Clinical trials in patients with previously untreated CML demonstrated that its efficacy in this setting was limited by substantial toxicity.\(^28\) Ponatinib continues to be evaluated in the frontline setting in ALL, and recent results from a trial in which it was combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) with alternating methotrexate and cytarabine demonstrated potential for long-term efficacy and safety.\(^29\)

BCR-ABL inhibitors have revolutionized the treatment of CML, with 5-year survival rates now approaching the level of the general population.\(^9\) Although they do not offer a traditional “cure”—in virtually all patients with clinical disease remission, BCR-ABL transcripts are still detectable—BCR-ABL inhibitors can lead to deep and durable reduction of these transcripts, a so-called deep molecular response, which allows many patients to discontinue treatment and enjoy a “functional cure.”\(^18\)

It was initially thought that only lifelong treatment could maintain functional cure, but several studies demonstrated that certain patients with a deep molecular response can stop long-term BCR-ABL inhibitor therapy without relapsing for significant periods of time.\(^10\) The European Stop Kinase Inhibitor trial, for example, demonstrated treatment-free remission for approximately half of patients being treated with any of the frontline BCR-ABL inhibitors.\(^8\) Numerous ongoing studies are examining this phenomenon, and the latest guidelines from the National...
Comprehensive Cancer Network suggest that stopping treatment with close monitoring is feasible in carefully selected patients.30

**IS THE BEST YET TO COME?**

Meanwhile, the development of BCR-ABL inhibitors continues to evolve, with several newer drugs and combinations in clinical trials (TABLE). Most notable is asciminib, the first allosteric inhibitor of BCR-ABL1, which capitalizes on the autoinhibitory function of the N-terminal cap of the ABL1 protein.11

When myristoylated, that cap binds to a pocket in the kinase domain, serving as an allosteric negative regulator of ABL function. The cap (and thus the autoinhibition) is lost in the fusion protein; asciminib is designed to bind to the empty pocket and restore inhibition of BCR-ABL kinase activity (FIGURE 2).11-14 In contrast to the more promiscuous ATP-competitive inhibitors, asciminib is a highly specific inhibitor of ABL kinases. Critically, it is also effective against T315I-positive CML.11,18,31

The results of a phase I study of asciminib in patients with CML were recently published (NCT02629692). A total of 150 patients with heavily pretreated disease were enrolled and treated with asciminib on either a once-daily schedule (n = 52) at doses of 80, 120, or 200 mg or a twice-daily schedule (n = 98) at doses of 10, 20, 40, 80, 150, 160, or 200 mg. Most of the participants (141; 94%) had chronic-phase CML, and 113 (80%) lacked the T315I mutation. Within this subset of 113 patients, 34 of 37 (92%) who did not have a complete hematologic response (CHR; defined as normalization of the complete blood count) at baseline achieved CHR during the study, and 31 of 57 patients (54%) without a complete cytogenetic response (CCyR; defined as the absence of Ph+ cells in the bone marrow) at baseline achieved CCyR in a median time of 24 weeks.

A major molecular response (MMR; defined as BCR-ABL1 transcript levels ≤0.1% on the International Scale) was achieved or maintained by 12 months in 48% of evaluable patients in this subset, including 57% with resistance to or intolerable toxicity from ponatinib. In contrast, 28% of patients with chronic-phase CML who had the T315I mutation achieved or maintained MMR by 12 months.11

Asciminib is also showing promise in combination with ATP-competitive inhibitors. Preliminary results from 34 patients enrolled in a phase I study (NCT02081378) evaluating the combination of asciminib with dasatinib or nilotinib in patients with CML resistant or intolerant to ≥2 prior BCR-ABL1 inhibitors were presented at the 24th Congress of the European Hematology Association (EHA 2019). Among patients who did not have BCR-ABL1 transcript levels <1% on the International Scale at baseline, 43% and 56% of patients in the nilotinib and dasatinib arms, respectively, achieved this by 48 weeks, and 31% and 36% of patients without MMR at baseline achieved MMR within this time frame.14

In a separate presentation at EHA 2019 (NCT02081378), the combination of asciminib and imatinib was also shown to be effective. Among the 25 heavily pretreated patients enrolled to date, the level of BCR-ABL1 transcripts was reduced to <1% in 60% of patients, to ≤0.1% (MMR) in 42%
TABLE. ABL Kinase Inhibitors in Clinical Development (continued)

<table>
<thead>
<tr>
<th>Drug (industry developer)</th>
<th>Ongoing Trials (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Third Generation</strong></td>
<td></td>
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<tr>
<td>Ponatinib (Iclusig) (Incyte)</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>• + reduced-intensity chemotherapy vs imatinib in newly diagnosed Ph+ ALL (NCT03989326)</td>
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<tr>
<td></td>
<td>• + decitabine and venetoclax in Ph+ AML or myeloid blast-phase CML (NCT04188405)</td>
</tr>
<tr>
<td></td>
<td>• + 5-azacitidine in accelerated- or blast-phase CML (NCT03895671)</td>
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<tr>
<td></td>
<td>• As second-line therapy in CML (NCT03807479)</td>
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<tr>
<td></td>
<td>• Followed by imatinib in chronic-phase CML (NCT04070443)</td>
</tr>
<tr>
<td></td>
<td>• In patients with CML or Ph+ ALL who progressed on prior TKIs or have T315I mutation (NCT02776605)</td>
</tr>
<tr>
<td></td>
<td>• + blinatumomab, methotrexate, and cytarabine in Ph+ BCR-ABL+, or relapsed/refractory ALL (NCT03263572)</td>
</tr>
<tr>
<td></td>
<td>• + high-intensity chemotherapy and blinatumomab in Ph+ and/or BCR-ABL+ ALL (NCT03147612)</td>
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<tr>
<td></td>
<td>• + combination chemotherapy in ALL (NCT01424982)</td>
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<tr>
<td></td>
<td>Phase I/II</td>
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<tr>
<td></td>
<td>• In pediatric recurrent/refractory leukemias or solid tumors (NCT03934372)</td>
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<tr>
<td></td>
<td>• + venetoclax and dexamethasone in Ph+ or BCR-ABL+ relapsed/refractory ALL or CML (NCT03574557)</td>
</tr>
<tr>
<td><strong>Allosteric Inhibitors</strong></td>
<td></td>
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<tr>
<td>Asciminib (ABL001) (Novartis)</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>• Versus bosutinib in chronic-phase CML previously treated with ≥2 TKIs (NCT03106779)</td>
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<tr>
<td></td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>• As addition to current nilotinib or dasatinib therapy in patients with Ph+ CML and MRD (NCT04216563)</td>
</tr>
<tr>
<td></td>
<td>• + imatinib in chronic-phase CML (NCT03578367)</td>
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<tr>
<td></td>
<td>• + other TKIs as frontline treatment for chronic-phase CML (NCT0396292)</td>
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<tr>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>• + dasatinib and prednisone in BCR-ABL+ B-ALL or blast-phase CML (NCT03595917)</td>
</tr>
<tr>
<td></td>
<td>• +/- other TKIs in CML or Ph+ ALL (NCT02081378)</td>
</tr>
</tbody>
</table>

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CML, chronic myeloid leukemia; Ph+, Philadelphia chromosome-positive; MDS, myelodysplastic syndrome; MRD, minimal residual disease; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

*Study is active but not currently recruiting patients.

All values are median unless otherwise noted.

*Radotinib is approved in South Korea under the trade name Supect.

and to ≤0.0032% in 15% by 48 weeks.

Asciminib combined with dasatinib and prednisone is also being tested in patients with newly diagnosed Ph+ ALL and CML, and results from the first 6 patients treated were detailed in a presentation at the 2019 American Society of Hematology (2019 ASH) Annual Meeting & Exposition (NCT03595917).13

Among other novel drugs are PF-114 and HQP1351, both ATP-competitive inhibitors designed to target the T315I mutation. An update on a phase 1 trial of HQP1351 in patients with treatment-resistant CML was presented at 2019 ASH. HQP1351 is administered once every other day in 28-day cycles at doses ranging from 1 mg to 60 mg. Among 101 patients enrolled, over a median follow-up of 12.8 months, HQP1351 was well tolerated, except at the 60-mg dose. Among 68 patients without CHR at baseline, 92.6% achieved CHR, and 60.5% of the 95 patients without CCyR at baseline achieved that goal.32

K0706 and radotinib are novel second-generation inhibitors that inhibit common BCR-ABL1 mutations but not T315I. The latter is approved in South Korea, and the recent RERISE study (NCT01511289) found that it may yield similar long-term OS and progression-free survival and higher MMR rates compared with imatinib in patients with newly diagnosed CML, as well as lower rates of treatment failure and grade 3/4 neutropenia and hypophosphatemia.33

Jane de Lartigue, PhD, is a freelance medical writer and editor based in Gainesville, Florida.

For a full list of references, see the article at OncLive.com.
Please refer to the full Prescribing Information for TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

- Are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1–stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or
- Are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
- Have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

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

Important Safety Information

Serious Adverse Reactions
Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

Immune-Mediated Pneumonitis
- Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, have occurred with TECENTRIQ treatment
- In clinical studies of TECENTRIQ as a single agent, 2.5% of patients developed pneumonitis, including Grade 3 (0.6%), Grade 4 (0.1%), and Grade 5 (<0.1%) events
- Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids followed by a taper. Withhold TECENTRIQ for Grade 2 and permanently discontinue for Grade 3 or 4 pneumonitis

Immune-Mediated Hepatitis
- Liver test abnormalities and immune-mediated hepatitis, including fatal cases, have occurred with TECENTRIQ treatment
- In clinical studies of TECENTRIQ as a single agent, hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (<0.1%) events
- Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of TECENTRIQ, including clinical chemistry monitoring. Administer corticosteroids followed by a taper for immune-mediated hepatitis. Withhold TECENTRIQ for AST or ALT elevations more than 3 and up to 8 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal. Permanently discontinue TECENTRIQ for AST or ALT elevations more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal

Immune-Mediated Colitis
- Immune-mediated diarrhea or colitis have occurred with TECENTRIQ treatment
- In clinical studies of TECENTRIQ as a single agent, diarrhea or colitis occurred in 20% of patients, including Grade 3 (1.4%) events
- Monitor patients for signs and symptoms of diarrhea or colitis. Withhold TECENTRIQ for Grade 2 or 3 and permanently discontinue for Grade 4 diarrhea or colitis

Immune-Mediated Endocrinopathies
- TECENTRIQ can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis and hypophysitis/hypopituitarism
- Withhold TECENTRIQ for Grades 2 to 4 endocrinopathies
- Thyroid Disorders
  - In clinical studies of TECENTRIQ as a single agent, hypothyroidism occurred in 4.6% of patients and hyperthyroidism occurred in 1.6% of patients
  - Monitor thyroid function prior to and during treatment with TECENTRIQ. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated
- Adrenal Insufficiency
  - In clinical studies of TECENTRIQ as a single agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (<0.1%) events
  - Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate corticosteroids and hormone replacement therapy as clinically indicated
- Type 1 Diabetes Mellitus
  - In clinical studies of TECENTRIQ as a single agent, type 1 diabetes mellitus occurred in <0.1% of patients
  - Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated
In 1L cisplatin-ineligible mUC (Cohort 1)

TECENTRIQ DELIVERED DURABLE RESPONSES

Durable responses demonstrated (median follow-up: 14.4 months)\(^1\)

\[
\begin{array}{c|c|c}
\text{ORR} & \text{DoR} \\
\hline
23.5\% & \text{MEDIAN DoR NOT REACHED} \\
\end{array}
\]

\(6.7\% \text{ CR} & 16.8\% \text{ PR} \)

\(n=28/119^*\); 95% CI, 16.2, 32.2

\(\text{• denotes censored value.}^{*}\)

\(\text{109 patients in Cohort 1 had missing or unavailable response status.}^{*}\)

\(\text{• 33\% ORR in patients with disease progression at least 12 months following neoadjuvant or adjuvant therapy (n=8/24*; 95\% CI, 16, 55)}^{1}\)

\(\text{• 2-year analysis data (median follow-up: 29.3 months): 24\% ORR (8\% CR, 16\% PR) (n=28/119*; 95\% CI, 16, 32)}^{1}\) with median DoR not reached (95\% CI, 30, 4\%)

TECENTRIQ offers flexible dosing options\(^1\)

\(\text{• TECENTRIQ can be administered as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks}^{\text{[W]}}\)

\(\text{[W]}\) was a pivotal Phase 3, multicenter, open-label, 2-cohort trial that included a cohort of 199 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients received TECENTRIQ 1200 mg IV q3w and were treated until unacceptable toxicity or disease progression. Major efficacy endpoints included ORR assessed by RI using RECIST v1.1 and DoR. Patients were considered cisplatin-ineligible if they met any one of the following criteria: impaired renal function (Ccr of 30 to 59 mL/min), ECOG PS of 4, hearing loss of ≥25 dB at 2 continuous frequencies, or grade 2 to 4 peripheral neuropathy.\(^{[W]}\)

\(\text{Note: [W] is an ongoing study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. Both cisplatin-eligible and cisplatin-ineligible patients are included in the study. The independent Data Monitoring Committee (IDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of <1% when treated with TECENTRIQ monotherapy had decreased survival in those who received platinum-based chemotherapy. The IDMC recommended closure of this TECENTRIQ monotherapy arm to further accrual of patients with low PD-L1 expression. There were no other changes recommended for the study, including any change in therapy for patients already randomized to and receiving treatment in the TECENTRIQ monotherapy arm.}\)

• In clinical studies of TECENTRIQ as a single agent, Grade 2 hypophysitis occurred in 0.1% of patients
• For Grades 2 to 4 hypophysitis, initiate corticosteroids and hormone replacement therapy as clinically indicated

Other Immune-Mediated Adverse Reactions

• TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system
• In clinical studies of TECENTRIQ as a single agent, or were reported in other products in this class, cardiac, dermatologic, gastrointestinal, general, hematological, musculoskeletal, neurological, ophthalmological, renal, and vascular immune-mediated adverse reactions occurred at an incidence of <1%.
• For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, withhold TECENTRIQ and administer corticosteroids. Permanently discontinue TECENTRIQ for Grade 4 immune-mediated adverse reactions involving a major organ.
• Evaluate for Vogt-Koyanagi-Harada syndrome if uveitis occurs in combination with other immune-mediated adverse reactions

Infections

• TECENTRIQ can cause severe infections including fatal cases
• In clinical studies of TECENTRIQ as a single agent, infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%) events
• Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable

Infusion-Related Reactions

• TECENTRIQ can cause severe or life-threatening infusion-related reactions
• In clinical studies of TECENTRIQ as a single agent, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%) events
• Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2 infusion-related reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion-related reactions

Embryo-Fetal Toxicity

• Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose

Nursing Mothers/Fertility

• Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose
• Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment

Most Common Adverse Reactions

The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ alone were fatigue (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. TECENTRIQ Prescribing Information. Genentech, Inc.

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Learn more at TECENTRIQ-HCP.com/mUC
This is a brief summary of information about TECENTRIQ. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

1.1 Advanced or Metastatic Non-Small-Cell Lung Cancer

TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) whose tumors express PD-L1 (PD-L1 tumor-infiltrating immune cells [IC] covering > 50% of the tumor area), as determined by an FDA-approved test (see Dosage and Administration [2.1]).

TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations before receiving TECENTRIQ.

1.2 Locally Advanced or Metastatic Triple-Negative Breast Cancer

TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small-cell lung cancer (NSQNSCLC) whose tumors express PD-L1 (PD-L1 tumor-infiltrating immune cells [IC] covering > 50% of the tumor area), as determined by an FDA-approved test (see Dosage and Administration [2.1]).

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

1.3 Small Cell Lung Cancer

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

2 CLINICAL STUDIES

2.1 Dosage and Administration

2.1.1 Advanced or Metastatic Non-Small-Cell Lung Cancer

In clinical studies enrolling 2616 patients who received TECENTRIQ in combination with platinum-based chemotherapy (see Clinical Studies [14.1]), patients with metastatic NSCLC and metastatic SCLC were randomized 1:1:2 to receive TECENTRIQ, atezolizumab, and one of three combinations of platinum and etoposide: P1 (cisplatin or carboplatin at the investigator’s discretion), P2 (cisplatin), and P3 (carboplatin).

In the P1 combination, TECENTRIQ was administered as a single-agent, followed by a taper for Grade 2 or higher pneumonitis or Grade 3 pulmonary infiltrate or interstitial lung disease, as determined by an FDA-approved test (see Dosage and Administration [2.1]).

The median duration of discontinuation of TECENTRIQ was based on the severity (see Dosage and Administration [2.1]).

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy (see Clinical Studies [14.1]), patients were randomized 1:1:1:1 to receive TECENTRIQ following pre-treatment with either pembrolizumab, nivolumab, durvalumab, or avelumab (see Other Antineoplastic Drugs [5.4]).

2.2 Dosing Schedule

TECENTRIQ is administered intravenously as a 1-hour infusion every 3 weeks. For patients with NSCLC, the recommended dose of TECENTRIQ is 840 mg/m². For patients with SCLC, the recommended doses of TECENTRIQ are 1200 mg/m² and 1680 mg/m² for ES-SCLC and SS-SCLC, respectively.

2.3 Concomitant Use

Concomitant use of TECENTRIQ or PDL1/PD-1 inhibitors with other antineoplastic drugs, hormone replacement therapy, or in combination with other antineoplastic drugs in NSCLC and SCLC.

5 ADVERSE REACTIONS

5.1 Immune-Mediated Pneumonitis

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, pneumonitis occurred in 5.5% of patients, including Grade 3 in 1.4% of patients. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids. The frequency and severity of pneumonitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.2 Immune-Mediated Hepatitis

In clinical studies enrolling 2616 patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC, hepatitis occurred in 9% of patients, including Grade 3 in 0.4% of patients. Systemic corticosteroids were required in 0.1% of patients and high-dose corticosteroids in 0.2% of patients. The frequency and severity of hepatitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.3 Immune-Mediated Colitis

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, colitis occurred in 4.3% of patients, including Grade 3 in 0.9% of patients. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids. The frequency and severity of colitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.4 Infusion-Related Reactions

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, the infusion-related reactions occurred in 5% of patients, including Grade 3 in 0.4% of patients. Systemic corticosteroids were required in 0.3% of patients and high-dose corticosteroids in 0.2% of patients.

5.5 Other Immune-Mediated Adverse Reactions

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, the following adverse reactions were reported in < 1% of patients who received TECENTRIQ as a single-agent and in 1242 patients who received TECENTRIQ in combination with platinum-based chemotherapy or were reported in other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

5.6 Hypersensitivity Reactions

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, the frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.7 Infusion-Related Reactions

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent, the frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.8 Embryo-Fetal Toxicity

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent, the frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

6 ADVERSE REACTIONS

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

• Immune-Mediated Pneumonitis (see Warnings and Precautions [5.2])
• Immune-Mediated Hepatitis (see Warnings and Precautions [5.3])
• Immune-Mediated Colitis (see Warnings and Precautions [5.4])
• Immune-Mediated Endocrine Abnormalities (see Warnings and Precautions [5.5])
• Infusion-Related Reactions (see Warnings and Precautions [5.7])
respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 1).

Tables 2 and 3 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 1).

Adverse reactions occurring in ≥ 10% of patients.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>0.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></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>0</td>
</tr>
</tbody>
</table>

1 Includes fatigue, asthenia, lethargy, and malaise
2 Includes edema peripheral, scrotal edema, lymphedema, and edema
3 Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
4 Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
5 Includes decreased appetite and early satiety
6 Includes rash, dermatitis, dermatitis acneform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
7 Includes urinary tract infection, urinary tract infection bacterial, cystitis, and ureopelvis
8 Includes cough and productive cough

Table 3: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>3</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
</tr>
</tbody>
</table>

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen (see Clinical Studies (14.1)). Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common Grades 3–4 adverse reactions (≥ 2%) were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%) and decreased appetite (27%). The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 1), a multicenter, open-label, single-arm trial that included 310 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except POPLAR. Among the 2616 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 29% were exposed for longer than 12 months.

One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression. The median duration of exposure was 15 weeks (0 to 87 weeks).

Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common Grades 3–4 adverse reactions (≥ 2%) were fatigue, diarrheal syndrome, nervous system disorder, dermatologic disorder, interstitial lung disease, diarrhea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia. Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

Adverse reactions occurring in ≥ 10% of patients with urothelial carcinoma in IMvigor210 (Cohort 2).

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>0.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
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<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>3</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
</tr>
</tbody>
</table>

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen (see Clinical Studies (14.1)). Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common Grades 3–4 adverse reactions (≥ 2%) were fatigue, diarrheal syndrome, nervous system disorder, dermatologic disorder, interstitial lung disease, diarrhea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia. Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

Adverse reactions occurring in ≥ 10% of patients with urothelial carcinoma in IMvigor210 (Cohort 2).

Table 3: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)
The safety of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naive patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.2)]. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

The most common Grades 3–4 adverse reactions (>2%) in patients receiving TECENTRIQ were fatigue/asthenia, hypertension, febrile neutropenia, diarrhea, pneumonia, nausea, decreased appetite, dehydration, and pulmonary embolism.

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

The most common Grades 3–4 adverse reactions (>2%) in patients receiving TECENTRIQ were fatigue/asthenia, nausea, decreased appetite, diarrhea, hypothyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hypertension, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

### Table 6: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin</th>
<th>Bevacizumab, Paclitaxel and Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 393</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>N = 394</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

### Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin</th>
<th>Bevacizumab, Paclitaxel and Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 609</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

### Table 8: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in OAK

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 578</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

### Table 9: Summary Laboratory Abnormalities in ≥1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 3)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 182</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

### Table 10: Summary Adverse Reactions in ≥1% of Patients with NSCLC Receiving TECENTRIQ in OAK

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 578</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

---

1. NCI CTCAE does not provide a Grades 3–4 definition for these laboratory abnormalities.

2. Includes cough and exertional cough

3. Includes fatigue and asthenia

4. Includes cough and exertional cough

5. Includes cough and exertional cough

6. Includes cough and exertional cough

7. Includes cough and exertional cough

8. Includes cough and exertional cough

9. Includes cough and exertional cough

10. Includes cough and exertional cough

### Table 12: Laboratory Abnormalities Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in OAK

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 609</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

### Table 13: Summary Adverse Reactions in ≥1% of Patients with NSCLC Receiving TECENTRIQ in OAK

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 578</td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
</tbody>
</table>

### Table 14: Summary Laboratory Abnormalities in ≥1% of Patients with NSCLC Receiving TECENTRIQ in OAK
of patients in the TECENTRIQ and paclitaxel protein-bound arm. Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse reaction leading to interruption of TECENTRIQ occurred in 31% of patients; the most common adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0–31.3 months) in the TECENTRIQ plus placebo protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0–25.1 months) in the placebo plus paclitaxel protein-bound arm. The most common Grades 3–4 adverse reactions occurring in >2% were neutropenia (8%), peripheral neuropathies (9%), neutrophil count decreased (4%), fatigue (4%), anemia (2.9%), hyperkalemia (2.2%), pneumonia (2.2%), and aspartate aminotransferase increased (2.0%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse reaction leading to TECENTRIQ discontinuation was peripheral neuropathy (<1%). Fatal adverse reactions occurred in 1.3% (6/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm; these included septic shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism. Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (>2%) were neutropenia, neutrophil count decreased, hyperkalemia, and pyrexia. Serious adverse reactions occurred in 23% (103/442) of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspepsia (1%), and pyrexia (1%). Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm.

Table 9: Laboratory Abnormalities Worsening From Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in OAK

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ (n=452)</th>
<th>Docetaxel (n=452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>67</td>
<td>3</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Hypoammonemia</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>decreased creatinine</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>23</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Graded according to NCI CTCAE version 4.0
2 Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546−585) and docetaxel (range: 532–560).
3 Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy

Table 10: Adverse Reactions Occurring in >20% of Patients with TNCB (IMpassion130)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ in combination with paclitaxel protein-bound (n=452)</th>
<th>Placebo in combination with paclitaxel protein-bound (n=438)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Back pain</td>
<td>15</td>
<td>1.3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Nanophagocytosis</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in >20% of Patients with TNCB (IMpassion130)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased Hemoglobin</td>
<td>79</td>
</tr>
<tr>
<td>Decreased Leukocytes</td>
<td>76</td>
</tr>
<tr>
<td>Decreased Neutrophils</td>
<td>58</td>
</tr>
<tr>
<td>Decreased Lymphocytes</td>
<td>54</td>
</tr>
<tr>
<td>increased Prothrombin IR</td>
<td>25</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for grade 1 events (NCI CTCAE v5.0). Graded based on the number of patients with available baseline and at least one on-treatment laboratory test. Small Cell Lung Cancer (SCLC)

The safety of TECENTRIQ in combination with paclitaxel protein-bound was evaluated in IMpassion130, a multicenter, international, randomized, double-blind, placebo-controlled trial in patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic disease (see Clinical Studies (14.3)). Patients received 840 mg of TECENTRIQ (n=452) or placebo (n=443) intravenously followed by paclitaxel protein-bound (100 mg/m2) intravenously for each 28-day cycle. TECENTRIQ was administered on days 1 and 15 and paclitaxel protein-bound was administered on days 1, 8, and 15 until disease progression or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to TECENTRIQ was 5.5 months (range: 0–32 months) and paclitaxel protein-bound was 5.1 months (range: 0–31.3 months) in the TECENTRIQ plus paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0–25.1 months) and paclitaxel protein-bound was 5.0 months (range: 0–23.7 months) in the placebo plus paclitaxel protein-bound arm. The most common adverse reactions leading to interruption of TECENTRIQ occurred in 59% of patients; the most common adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%). Fatal adverse reactions occurred in 2% of patients receiving TECENTRIQ. These included pneumonia, cardiac arrest, shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism. Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (2%) were neutropenia, neutrophil count decreased, hyperkalemia, and pyrexia. Serious adverse reactions occurred in 23% (103/442) of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspepsia (1%), and pyrexia (1%). Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common Grades 3–4 adverse reactions occurring in >2% were neutropenia (8%), peripheral neuropathies (9%), neutrophil count decreased (4%), fatigue (4%), anemia (2.9%), hyperkalemia (2.2%), pneumonia (2.2%), and aspartate aminotransferase increased (2.0%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse reaction leading to TECENTRIQ discontinuation was peripheral neuropathy (<1%). Fatal adverse reactions occurred in 1.3% (6/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm; these included septic shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism. Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (2%) were neutropenia, neutrophil count decreased, hyperkalemia, and pyrexia. Serious adverse reactions occurred in 23% (103/442) of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspepsia (1%), and pyrexia (1%). Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common Grades 3–4 adverse reactions occurring in >2% were neutropenia (8%), peripheral neuropathies (9%), neutrophil count decreased (4%), fatigue (4%), anemia (2.9%), hyperkalemia (2.2%), pneumonia (2.2%), and aspartate aminotransferase increased (2.0%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 59% of patients; the most common adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%). Adverse reactions leading to interruption of TECENTRIQ occurred in 59% of patients; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.9%), infusion-related reaction (3.3%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).
Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

### Table 12: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ with Carboplatin and Etoposide N = 198</th>
<th>Placebo with Carboplatin and Etoposide N = 196</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades1 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthma</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

### Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Carboplatin and Etoposide1</th>
<th>Placebo with Carboplatin and Etoposide1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades1 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>94</td>
<td>17</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>73</td>
<td>45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Decreased TSH</td>
<td>28</td>
<td>NA3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Increased Lactate Dehydrogenase</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>37</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

**8 USE IN SPECIFIC POPULATIONS**

### 8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action (see Clinical Pharmacology (12.3)), TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death (see Data). Advise females of reproductive potential of the potential risk to a fetus.

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

**Data**

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

**8.2 Lactation**

**Risk Summary**

There is no information regarding the presence of atezolizumab in human milk, the effects on the breast infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

### 8.3 Females and Males of Reproductive Potential

**Prescribing Information**

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ (see Use in Specific Populations (8.3)).

**Conception**

Females

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)). Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

**Infertility**

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment (see Nonclinical Toxicology (13.5)).

### 8.4 Pediatric Use

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

**8.5 Geriatric Use**

Of 2481 patients with urothelial carcinoma, lung cancer, and triple-negative breast cancer who were treated with TECENTRIQ in clinical studies, 45% were 65 years and over and 11% were 75 years and over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older, and younger patients.

### 17 PATIENT COUNSELING INFORMATION

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

**Immune-Mediated Adverse Reactions**

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath (see Warnings and Precautions (5.1)).
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding (see Warnings and Precautions (5.2)).
- Nephritis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stool, or severe abdominal pain (see Warnings and Precautions (5.3)).
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypohyperthyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis (see Warnings and Precautions (5.4)).
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions (see Warnings and Precautions (5.5)).

**Infections**

Advise patients to contact their healthcare provider immediately for signs or symptoms of infection (see Warnings and Precautions (5.6)).

**Embryo-Fetal Toxicity**

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions (5.7)). Use in Specific Populations (8.1, 8.3).

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ (see Use in Specific Populations (8.3)).

**Lactation**

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose (see Use in Specific Populations (8.3)).

**References**

Manufactured by:
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A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
PDL/080916/01936
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Although considerable progress has been made in treating diffuse large B-cell lymphoma (DLBCL) since the advent of chemoimmunotherapy, approximately 33% of patients still develop relapsed/refractory (R/R) disease, which is associated with considerable morbidity and mortality. Several treatment options exist for this patient population including high-dose therapy and transplant, as well as chimeric antigen receptor (CAR) T-cell therapy. However, as patients progress through treatments, options in subsequent lines of therapy dwindle, particularly if they are ineligible for transplant. This dilemma has led to the search for novel therapeutic approaches for patients whose disease fails to respond to currently available therapies.

Fresh Options Are Emerging for Relapsed DLBCL

by CHRISTINA T. LOGUIDICE

One approach that can be considered for patients with R/R DLBCL is bendamustine-rituximab (BR) in combination with the novel antibody-drug conjugate polatuzumab vedotin-piiq (Polivy). The regimen was granted accelerated approval by the FDA on June 10, 2019, making it the first chemoimmunotherapy approved for these patients. Approval was based on the results of Study GO29365 (NCT02257567), which included 25 patients who achieved a CR or partial response (PR) in the BR plus polatuzumab vedotin arm, 16 (64%) had a duration of response (DOR) of ≥6 months and 12 (48%) had a DOR of ≥12 months. BR plus polatuzumab vedotin is currently indicated for adult patients with DLBCL that has progressed or returned after ≥2 prior therapies.

Peter Martin, MD, said another novel combination showing promise is ibrutinib (Imbruvica)–lenalidomide (Revlimid)–rituximab (Rituxan) (iR2 regimen). This triplet is being evaluated in the ongoing, multicenter, open-label, phase II PCYC-1123 study (NCT02077166), which...
is evaluating 89 patients with R/R non-germinal center B-cell-like (non-GCB) DLBCL who are ineligible for stem cell transplantation. Participants receive oral lenalidomide 20 mg (n = 55) or 25 mg (n = 34) on days 1 to 21 of each 28-day cycle plus ibritunumab 560 mg orally once daily and rituximab 375 mg/m² intravenously on day 1 of cycle 1 to 6. The median time to response was 2.7 months. Of the 85 response-evaluable patients with follow-up response assessment, the overall response rate (ORR) was 47%, including 28% CRs and 19% PRs. “This regimen clearly has activity,” Martin said, noting that he has occasionally used it off-label.

When trying to offer patients palliation of symptoms, Martin said he sometimes uses single-agent chemotherapy, such as gemcitabine or bendamustine. “Anecdotally, I think that we’ve also tried a variety of gemcitabine or bendamustine. Anecdotally, uses single-agent chemotherapy, such as gemcitabine or bendamustine. “Anecdotally, I think that we’ve also tried a variety of things, including HDAC [histone deacetylase] inhibitors, demethylating agents. Periodically, people get responses to some of these things, and although it’s hard to say that that’s the right thing to do all the time, we will always have examples of somebody who does well,” he said. “Some of these patients with large cell lymphoma seem to have a lymphoma that does not explode but rather trickles. Those are opportunities to try creative things. My bias is always to do that in the context of a clinical trial, but it’s not always feasible,” he added.

Novel approaches to maintain disease control in ASCT candidates with more aggressive disease is another area of need. Use of immunotherapy following ASCT is being explored, as patients with high-risk disease often progress within the first 18 months after ASCT, and maintenance strategies have thus far failed to demonstrate benefit. The ongoing CPIT-001 trial is assessing the safety and efficacy of combined checkpoint inhibition with ipilimumab (Yervoy) and nivolumab (Opdivo) as consolidation following ASCT for patients with high-risk hematological malignancies, including primary refractory DLBCL or relapse <12 months after completion of induction.

“It’s a small number of patients—15 primary refractory patients or early relapse. The patients with EFS [event-free survival] at 18 months is 83%,” moderator Andre Goy, MD, said. He noted that a challenge with immunotherapy is the toxicity. Among the entire study population, which also included patients with multiple myeloma and peripheral T-cell lymphoma, 65% of patients developed immune-related adverse effects (irAEs) grade ≥2, requiring treatment with systemic steroids. The most common irAEs included colitis, rash, thrombocytopenia, anemia, and transaminitis. There was 1 death from treatment-related pneumonitis. Although steroid use is thought to compromise the efficacy of immunotherapy, neither its use nor the length of its use affected progression-free survival or overall survival (OS).

**TAFASITAMAB AND THE L-MIND STUDY**

An exciting study that the panelists discussed is the ongoing, open-label, single-arm, phase II L-MIND trial (NCT02399085), which is assessing tafasitamab (MOR208) plus lenalidomide in patients with R/R DLBCL treated with ≤3 prior lines of therapy, including at least 1 anti-CD20 therapy, who were ineligible for stem cell transplantation. Tafasitamab is an Fc-enhanced, humanized, anti-CD19 monoclonal antibody that has previously shown single-agent activity in this patient population. Interestingly, there were a few complete responses—complete remissions in diffuse large B-cell lymphoma—which you don’t typically see with antibody therapy alone,” panelist Kami J. Maddocks, MD, said. These promising data led to the L-MIND study, which assessed the efficacy of tafasitamab and lenalidomide combination therapy for 1 year, with patients allowed to continue tafasitamab alone thereafter if they achieved stable disease or better. The study’s primary end point was independent review committee-assessed ORR as per Cheson 2007 criteria. The ORR in these 80 patients was 60%, with a 42% complete remission rate. The median duration of response was 22 months,” Maddocks said.

Overall, the tafasitamab and lenalidomide combination was well tolerated. “The toxicity was primarily what you see with lenalidomide alone,” Maddocks said. The most commonly reported adverse effects (AEs) were infusion reactions, and serious treatment-related AEs were usually infections and neutropenic fever. “About 50% of patients had dose reductions in the lenalidomide, but 70% of them were maintained at a dose of 20 mg or higher,” she said, noting that once the lenalidomide was stopped after 12 months, the toxicity significantly decreased.

Subgroup analyses of the L-MIND trial showed a trend for better outcomes among patients with 1 prior line of therapy versus those with ≥2 prior lines, with an ORR of 70% versus 50%, respectively, and a 12-month OS rate of 86.9% and 60.1%, respectively. However, the number of prior lines of therapy did not affect DOR. As was also expected, patients with a low or low-intermediate International Prognostic Index score had better outcomes than those with an intermediate-high or high score, with an ORR of 70.0% versus 50.0%, respectively; a 12-month DOR rate of 86.5% versus 50.4%, respectively; and a 12-month OS rate of 87.0% versus 59.9%, respectively. This was done in a transplant-ineligible population and in a non-GC [nongerminal center subtype] compared to the GC subtype, but the GC subtype still had a 50% overall response rate,” Maddocks said.

There has been some concern that tafasitamab may interfere with the effectiveness of subsequent use of CD19-targeted CAR T-cell therapy due to competition for CD19 binding. “We don’t have great data on this,” Maddocks said, but noted that an abstract presented at the 2019 American Society of Hematology Annual Meeting (2019 ASH) outlining in vitro assessments suggests CAR T-cell therapy is still effective in cells that have been treated with tafasitamab. There are also a few patients who were treated on trial who went on to get CAR T and have done well on that therapy. But, certainly, using it either before or even after the CAR T is something that we’ll
There are over 2000 new drugs in the pipeline of lymphoma, so we have a lot of work in front of us. Please enroll and refer patients for clinical trials. This is the way we move the needle.”

—Andre Goy, MD

have to have more patients treated with to understand the effects,” she said.

The panelists discussed when they may consider using tafasitamab in clinical practice versus CAR T-cell therapy. “There are some patients who I would not be too comfortable giving CAR T-cell therapy, especially patients with some type of organ dysfunction. That would be a very nice population that you would still want to consider something like this for,” panelist Nathan H. Fowler, MD, said. Maddocks also pointed out that there are parts of the United States where it would be challenging for patients to receive CAR T-cell therapy, such as those who live in rural settings and cannot easily travel, and that tafasitamab regimen could be considered for such patients as well.

BISPECIFIC ANTIBODIES
One class of agent with numerous promising drugs in various stages of clinical development are bispecific antibodies, which combine ≥2 antigen-recognizing elements into a single construct that can bind to ≥2 targets. Because of this mechanism, “[bispecific antigens] potentially could do similar things that we see with CAR T cells,” panelist Nathan H. Fowler, MD, said, noting that he is particularly excited by T-cell redirecting bispecific antibodies. “They’re using your own CAR T cells, drawing them to the tumor, and hopefully inducing this T-cell response,” he said.

A bispecific antibody that has received a great deal of attention recently is REGN1979, which targets both CD20 and CD3. At 2019 ASH, a very high response rate was reported in patients with relapsed or refractory DLBCL who received ≥80 mg of REGN1979. The ORR was 57.9% and the CR rate was 42.1%. When examining response based on prior CAR T-cell exposure, patients who did not receive prior CAR T-cell therapy had an ORR of 71.4%, all of which were CRs. In contrast, patients who received prior CAR T-cell therapy had an ORR of 50.0%; 25% had CRs and 25% had PRs.

The lower response rates in heavily pretreated patients, particularly in those who have received previous CAR T-cell therapy, are not surprising because bispecific antibodies rely on patients’ T cells, which are more likely to be compromised in this patient population than in those who have received few or no prior treatments. Nevertheless, it is promising that some CRs were still observed in the more heavily pretreated patients.

Another exciting bispecific antibody is mosunetuzumab, which has also yielded some CRs in patients with heavily pretreated relapsed or refractory DLBCL, including disease progression after CAR T-cell therapy. Mosunetuzumab targets CD3 on the surface of T cells and CD20 on the surface of B cells. Among 16 patients who were efficacy evaluable and had prior CAR T-cell therapy (7 DLBCL, 5 transformed follicular lymphoma [FL], 4 FL), the ORR and CR rates were 43.8% (n = 7) and 25% (n = 4; 2 DLBCL and 2 FL), respectively.

IMPORTANCE OF CLINICAL TRIALS
Throughout the Peer Exchange, the panelists emphasized the importance of enrolling patients into clinical trials. “There are over 2000 new drugs in the pipeline of lymphoma, so we have a lot of work in front of us. Please enroll and refer patients for clinical trials,” Goy said. “This is the way we move the needle,” he added.

Martin emphasized that patients who participate in clinical trials often have superior outcomes. “I think that we have to make more of an effort as a research community to bring clinical trials to populations that historically have not had access to them. I think that all of us have looked recently at a funding opportunity from the Leukemia & Lymphoma Society, which rightfully perceives this as a weakness,” he said.

Fowler identified some problems regarding how clinical research is being performed. “We are incredibly inefficient in the way we conduct clinical research across the world. Right now, there’s a major gap in the biological understanding of these diseases and what we do in clinical practice…I think some of that has to do with the lack of mechanistic and correlative studies that occur in our clinical trials,” he said.

The panelists acknowledged, however, that it is currently difficult to enroll some patients into trials, such as individuals who relapse after CAR T-cell therapy. “The problem is [these patients] usually have other issues like thrombocytopenia, and they are not eligible for trials,” panelist Julio Chavez, MD, MS, said. Nowakowski concurred. “I think you nailed it because this is a very difficult population to deal with. But we are living in a post-CAR T-cell world—they are here, and they’re probably going to be around for some time—so we need to learn how to deal with those patients who are relapsing post-CAR T-cell therapy. Since we are developing our future clinical trials, we must be open-minded when defining the inclusion criteria,” he concluded.
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[1] The Primary Endpoint of Overall PFS was not met in this study.


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