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Anis Hamid, MBBS, on Hormone-Sensitive PROSTATE Cancer
Heather A. Wakelee, MD, on NSCLC Priorities

CARBONE CANCER CENTER
Hematopoietic Stem Cell Transplant: A Viable Option for Older Patients With AML
BY MARK B. JUCKETT, MD
The efficacy of XOSPATA was established on the basis of CR\(^\dagger\) or CRh,\(^\dagger\) the duration of CR/CRh (DOR), and the rate of conversion from transfusion independence at the first interim analysis\(^1\):

- **36% reduced risk of death with XOSPATA (n=247)** vs salvage chemotherapy (n=124)
  - 9.3 months median OS (95% CI: 7.7, 10.7) vs 5.6 months with salvage chemotherapy (95% CI: 4.7, 7.3)
  - HR=0.64 (95% CI: 0.49, 0.83); \(P=0.0004\)

**21% CR/CRh**
(95% CI: 14.5, 28.8; n=29/138)
- The median DOR was **4.6 months** with XOSPATA (range: 0.1 to 15.8; n=29/138)
  - DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type. Deaths were counted as events
- Among patients in the XOSPATA arm who were transfusion dependent at baseline (n=106), **31.1%** became transfusion independent with XOSPATA during any 56-day post-baseline period (n=33/106)

- Transfusion independence is defined as patients who were dependent on RBC and/or platelet transfusions at baseline and became independent of RBC and platelet transfusions during any 56-day post-baseline period

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\(^2\))\(^3\):

- 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 FLT3m+ AML\(^1,3\)
- The efficacy of XOSPATA was based on an interim analysis and a final analysis\(^1\):
  - 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

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**Notes:**
- FLT3 mutation status: FLT3-ITD, FLT3-TKD, and FLT3-ITD-TKD.\(^1\)
- 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.\(^1\)
- CR defined as normal marrow differential with <5% blasts, ANC \(\geq 1.0 \times 10^9/L\) and platelets \(\geq 100 \times 10^9/L\), no evidence of extramedullary leukemia, and must have been RBC and platelet transfusion independent.\(^1\)
- CRh defined as marrow blasts <5%, partial hematologic recovery, ANC \(\geq 0.5 \times 10^9/L\) and platelets \(\geq 50 \times 10^9/L\), no evidence of extramedullary leukemia, and could not have been classified as CR.\(^1\)
- Response was ongoing.\(^3\)

AML=acute myeloid leukemia; ANC=absolute neutrophil count; CI=confidence interval; CR=complete remission; CRh=complete remission with partial hematologic recovery; FLT3=FMS-like tyrosine kinase 3; HR=hazard ratio; ITD=internal tandem duplication; m+=mutation-positive; NCCN=National Comprehensive Cancer Network; OS=overall survival; RBC=red blood cell; TKD=tyrosine kinase domain.

**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\(^4\)) for Acute Myeloid Leukemia V3.2020. © 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.

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, hypotenison, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome (See BOXED WARNING) 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotenison, 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 (QTc 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 phosphatase decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

Drug Interactions

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

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

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

Specific Populations

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

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

**WARNING: DIFFERENTIATION SYNDROME**

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction.

If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

**INDICATIONS AND USAGE**

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

**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 at the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

**Dose Modification**

Assess blood counts and blood chemistries, including creatine phosphokinase, prior to the initiation of XOSPATA, at least once weekly for the first month, 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 and reduce XOSPATA dosage in patients who have a QTcF greater than 500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Differentiation Syndrome**

Of 319 patients treated with XOSPATA in the clinical trials, 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, 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).

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

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

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

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

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

Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased...
48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms of differentiation syndrome may recur with premature discontinuation of resolution of symptoms and administer corticosteroids for a minimum of 3 days. 

**Pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, or fatal if not treated.** Symptoms of differentiation syndrome in patients treated with XOSPATA may be life-threatening due to proliferation and differentiation of myeloid cells.

**CONTRAINDICATIONS**

- Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA.
- Select patients for the treatment of AML with XOSPATA based on the presence of FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) mutations.
- 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 intolerance, the dose may be increased to 180 mg orally once daily in patients who tolerate the initial dose.

**Selected Patients**

The following is a brief summary of full Prescribing Information. Please see the full Prescribing Information for complete information on dosing and administration.

**Patient Selection**

- If differentiation syndrome is suspected, initiate corticosteroid therapy. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA.

**Differentiation Syndrome**

- The following are the most common adverse reactions leading to dose interruption: dyspnea, pleural effusion, pericardial effusion, hypotension, tachycardia, edema, rash, and hypertension. The most frequent adverse reactions leading to dose interruption and causing discontinuation of XOSPATA were dyspnea (13%), pleural effusion (13%), and hypotension (10%).

**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. Do not 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 4 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.

**Pregnancy**

- Safety and effectiveness in pediatric patients have not been established.

**Geriatic 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**

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

Early findings from the first US clinical trial evaluating therapy genetically altered with CRISPR editing in patients with cancer show why the technology has been generating such excitement in oncology. Experts discuss the implications of the University of Pennsylvania research and the status of other ongoing efforts.

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By Maurie Markman, MD

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Rising to the COVID-19 Challenge

CAN THE INNOVATIVE SPIRIT that has powered so many advancements in oncology care over the past several decades help the healthcare field confront the dire threat posed by coronavirus disease 2019 (COVID-19)? The oncology community is already rising to the challenge and early signals suggest that the infrastructure that has supported so many improvements in cancer care will contribute significantly to the response to the pandemic.

In the United States, the incidence rate and the number of deaths from COVID-19 have grown precipitously since early March. Any statistic we could cite here becomes outdated and more alarming within 24 hours. Before that grim toll started climbing, leading experts in the oncology care and drug development arenas began applying their considerable knowledge to COVID-19. Just as the pandemic has affected all areas of our lives, COVID-19 has permeated the oncology field. In the United States, the incidence rate and the number of deaths from COVID-19 have grown precipitously since early March. Any statistic we could cite here becomes outdated and more alarming within 24 hours. Before that grim toll started climbing, leading experts in the oncology care and drug development arenas began applying their considerable knowledge to COVID-19. Just as the pandemic has affected all areas of our lives, COVID-19 has permeated the oncology field.

In his column, Maurie Markman, MD, our editor in chief, discusses COVID-19 in the context of other serious public health threats facing our nation. We are heartened by the swift and thoughtful response to COVID-19 displayed by so many oncology leaders. Our editorial team is committed to bringing you vital information on the pandemic as it unfolds. OncLive.com provides a wealth of articles and up-to-the-minute news helpful to practicing oncology specialists.

Meanwhile, in the chaos of the moment, we find comfort in pondering the words of Louis Pasteur, the great French chemist who created and tested vaccines for many diseases during the 1800s. “In the field of observation, chance favors only the prepared mind.”

The oncology community is ready, willing, and very able to help.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
Cancer hits hard in Kentucky. That’s why, every day, the team at Markey steps up, with research projects that include decoding an enzyme that may be behind some resistant strains of prostate cancer. Because we’re not just treating cancer today. We’re working hard to beat it once and for all.

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From the Editor

Public Health Sector Groans Under Burden of Multiple Epidemics

by MAURIE MARKMAN, MD

This has been a difficult time for public health policy and regulatory organizations struggling to deal with rapidly changing and unquestionably serious societal health-related issues and concerns. The list of problems these agencies must tackle is growing, and so are the questions about the strategies that should be used to address these threats.

Let’s start with the mini-epidemic of vaping-related severe lung toxicity cases, which still are not completely understood; there have been more than 2800 cases, with 68 deaths, from the time the illnesses were first noted in August 2019, through mid-February 2020.1,2 Because of the expanding use of e-cigarette products in the United States, public health and regulatory agencies must quickly and carefully consider how such toxicities can be prevented in the future, especially with knowledge that legal, illegal, and completely unknown products are increasingly being directly inhaled into the lungs.3

Additionally, the daily news related to the spread of coronavirus disease 2019 (COVID-19) across the world, including in the United States, raises questions about how prepared government agencies and hospital facilities are for the widespread introduction of a new, highly infectious viral agent, capable of causing serious illnesses in tens of thousands, if not millions, of people worldwide.

If our ability, as a society, to motivate the population to be vaccinated against seasonal influenza is any indication, concern is legitimately heightened for how we will effectively deal with COVID-19 in this country. So far this influenza season, there have been at least 38 million illnesses, 390,000 hospitalizations, and 23,000 deaths from influenza nationwide, according to the Centers for Disease Control and Prevention.4

Although not as immediate a threat as the previously described illnesses, the stunning increase in the overall incidence of obesity in the United States is another pressing public health concern. Findings from a recently reported study indicate that by the year 2030, one-half of all adults in this country will be considered obese (body mass index [BMI], ≥30).5 Perhaps of even greater concern, investigators predict that almost 1 in 4 adults is projected to fall into the category of severe obesity (BMI, ≥35) by the same date. The implications of these statistics are simply staggering for the almost certain dramatic increase in diabetes, cardiac disease, and obesity-related malignancies, including cancers of the breast (post menopausal), endometrium, colon, esophagus, pancreas, thyroid, kidney, liver, and gall bladder.

It should be noted that these percentages are not projected to affect the population of this country equally. Unfortunately, it is the members of our society near or below the poverty threshold (annual income, <$20,000) who are at greatest risk of experiencing severe obesity—almost one-third of this population, compared with approximately 22% of individuals with a higher annual household income (≥$50,000).4 And, the group of lower-income individuals is the least likely to be able to modify diets and change other behaviors that heighten the risk of obesity.

The ongoing opioid epidemic in the United States is also relevant—specifically, the role physicians have had in helping to create this major societal health-related problem and, hopefully, subsequently control it moving forward. A provocative recent report regarding opioid prescribing patterns found that 1% of physicians in this country were responsible for fully 49% of all opioid doses. Further, this group accounted for 27% of the total number of prescriptions written.6

These data are clearly relevant to the oncology physician. Many have noted that the well-intentioned but unfocused attempts by regulatory agencies to control inappropriate opioid use has the potential to cause harm to a critical segment of the population of patients with cancer (eg, those receiving hospice and end-of-life palliative care) who may require regular and frequent
administration of moderate or large doses of opioid medications to ensure adequate and essential pain control.

**WHAT SHOULD THE FDA DO?**

Although this commentary can barely scratch the surface of the multiple complex issues involving regulatory agencies, we should consider what role the FDA should play in these major societal health-related concerns. What should be the FDA’s focus in the future, from regulating tobacco and vaping products; to ensuring public safety; to permitting companies to market products, such as nutritional supplements for weight reduction, they claim favorably affect health?

The critical role of the FDA in multiple areas cannot be overstated. Even an area as apparently mundane as the general safety of sunscreens, and the various claims made by the manufacturers of those products, requires scrutiny by this agency. Of course, the value of reducing the risks associated with excessive direct sun exposure with the goal of preventing skin cancers is a clear and unquestionable benefit associated with their routine and regular use. But are these products actually safe? Findings from a recent report raised this question and possible concern. Investigators evaluated 6 active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) in 4 sunscreen formulations and found that all were measured within plasma at concentrations that "surpassed the FDA threshold for potentially waiving some of the additional safety studies for sunscreens."7

Although it would be inappropriate to conclude that these products are unsafe based on these limited data, it would be equally unwise to declare that these widely used items are completely safe. It should be the responsibility of the FDA to work with the manufacturing community to provide a clear answer to the public.

**REFERENCES**

**FDA Digest**

**Nivolumab/Ipilimumab Gets Approval for Advanced HCC**

The treatment choices for patients with hepatocellular carcinoma (HCC) have broadened with the accelerated approval of nivolumab (Opdivo) in combination with ipilimumab (Yervoy) for those who previously received sorafenib (Nexavar).

The approval is based on cohort findings from the phase I/II CheckMate040 study (NCT01658878), in which the doublet regimen induced an objective response rate (ORR) of 33% (95% CI, 20%-48%) in this patient population at a median follow-up of 28 months. This included an 8% complete response (CR) rate and a 24% partial response (PR) rate.

The duration of response ranged from 4.6 to 30.5-plus months, with 88% of responses lasting ≥6 months; 56%, ≥12 months; and 31%, ≥24 months. In an analysis by blinded independent central review, the ORR was 35% (95% CI, 22%-50%), with a 12% CR rate and a 22% PR rate.

The combination regimen’s approval in this setting is contingent on the results of a confirmatory trial.

TO READ MORE, VISIT onclive.com/link/7536.

**EGFR-MET Antibody Secures Breakthrough Status in NSCLC**

JNJ-61186372 (JNJ-6372), a novel bispecific antibody, received a breakthrough therapy designation for the treatment of patients with EGFR-positive metastatic non–small cell lung cancer (NSCLC) who harbor exon 20 insertion mutations and whose disease progressed on or after platinum-based chemotherapy.

The agent demonstrated its efficacy in a phase I trial (NCT02609776), in which treatment with JNJ-6372 elicited preliminary responses in this patient population with a manageable safety profile. Investigators of the first-in-human study are evaluating JNJ-6372 as a monotherapy and combined with lazertinib, an EGFR tyrosine kinase inhibitor, in approximately 400 adults with advanced NSCLC.

As of January 17, 2019, 116 patients were enrolled and received treatment. Results showed that 28% of the 88 patients evaluated for a response achieved best-time-point response of partial response (PR). Several (6 of 20) patients with exon 20 insertions had best-time-point response of PR, with 3 confirmed, investigators said.

TO READ MORE, VISIT onclive.com/link/7534.

**FDA Clears Next-Generation Cytology Test for Cervical Cancer Detection**

Roche’s CINtec PLUS Cytology test is newly cleared for use in women whose primary cervical cancer screening yields positive results for the human papillomavirus (HPV), as detected by the cobas 4800 HPV Test.

The next-generation cytology test, which simultaneously detects p16 and Ki-67 to identify women whose HPV infections are most likely to be associated with cervical precancers, is the first biomarker-based test specifically approved for use in women with HPV-positive/Pap cytology-negative cotesting results. When a cell expresses both p16 and Ki-67, it is highly likely that the patient has transforming HPV infections that could progress to precancer or cancer.

By providing definitive information about which HPV-positive women would likely benefit most from immediate referral to colposcopy versus repeat testing, Roche stated, CINtec PLUS Cytology can streamline care, helping clinicians direct women to the appropriate diagnostic procedures before their disease progresses to a more advanced stage.

The approval was supported by data from the registrational IMPACT (Improving Primary screening And Colposcopy Triage) trial, in which investigators evaluated the test as a triage tool in several screening scenarios among more than 35,000 women. Data have not been published, Roche stated, adding that it expects the test to be widely available in the United States later this year.

TO READ MORE, VISIT onclive.com/link/7536.

**Breakthrough Device Designation May Expand HCC Toolkit**

The Elecsys GALAD score will receive expedited development and review as a result of a breakthrough device designation for the diagnosis of early-stage hepatocellular carcinoma (HCC). The algorithmic score is a serum biomarker-based tool designed for use with ultrasound, which is widely used to check α-1-fetoprotein (AFP) levels. In chronic liver diseases including hepatitis and cirrhosis, AFP can be chronically elevated, indicating the potential presence of AFP-producing tumors associated with HCC.

Although other methods of assessing AFP, such as liver biopsy and abdominal computed tomography scans, are more invasive than ultrasound, they may offer a more accurate alternative. Data from a recent meta-analysis suggested that ultrasound may miss ≥50% of early-stage HCCs.

When used in tandem with ultrasound, the Elecsys GALAD score, which combines gender and age with biomarker results of the Elecsys AFP, AFP-L, and PIVKA-II tests to project risk, may facilitate earlier detection of HCC, potentially improving patient outcomes while offering a minimally invasive, more cost-effective option for evaluation, according to Roche, the score’s developer.

TO READ MORE, VISIT onclive.com/link/7558.

**COVID-19**

**Trial Will Test Oncology Support Drug as COVID-19 Intervention**

Tocilizumab (Actemra), an interleukin-6 (IL-6) receptor antagonist, will be evaluated as a therapeutic option for patients with coronavirus disease 2019 (COVID-19) in the phase III COVACTA trial, according to Genentech, the drug’s developer. The agent is currently approved for the treatment of severe or life-threatening cytokine release syndrome caused by chimeric antigen receptor T-cell therapy.

The first global study of tocilizumab in this setting, COVACTA will enroll approximately 300 adults hospitalized with COVID-19 beginning this month. Investigators will randomize patients to tocilizumab plus the standard of care (SOC) or SOC alone. COVACTA’s primary and secondary end points include clinical status, mortality, mechanical ventilation, and intensive care unit variables. Patients will be followed for 60 days after randomization, after which an interim analysis will be conducted to assess early efficacy.

Genentech is initiating the trial in collaboration with the Biomedical Advanced Research and Development Authority, which is part of the US Health and Human Services Office of the Assistant Secretary for Preparedness and Response. COVACTA is among several other clinical studies of tocilizumab in this patient population, according to Genentech, who added that data on the agent’s safety and efficacy in the treatment of COVID-19 is limited.

Of note, China’s National Health Commission has added tocilizumab to its diagnosis and treatment plan for COVID-19.

TO READ MORE, VISIT onclive.com/link/7593.
Over 50% of Multiple Myeloma patients see their Primary Care/Internal Medicine physicians at first presentation of symptoms (unexplained bone pain, anemia, etc.)

When Primary Care and Internal Medicine physicians follow Guideline Compliant Testing, Multiple Myeloma patients can be identified earlier. It is vital to diagnose these patients early so they can be referred to the hematologist-oncologist, and prevent future complications.

Only Freelite® is referenced in over 3,000 publications, mentioned by name in the IMWG guidelines, and FDA cleared for both diagnosis and monitoring of Multiple Myeloma and AL Amyloidosis.

Visit [www.ThinkFreelite.com/hematology](http://www.ThinkFreelite.com/hematology) to learn more.


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THE RAPID EVOLUTION OF Coronavirus disease 2019 (COVID-19) has required institutions to adopt pandemic-specific protocols to minimize the potential for virus exposure and transmission. Broadly, these preventive measures have included travel restrictions for faculty and staff, as well as putting COVID-19 screening procedures in place for patients seeking care at oncology clinics. The risk that COVID-19 poses for patients with cancer, many of whom are receiving immunosuppressive therapies such as mTOR inhibitors, has been a key question for clinicians, particularly because infectious diseases are the second-leading cause of mortality among this subgroup of the American population.1

In recent interviews, members of the OncologyLive® advisory board discussed how COVID-19 has affected their patient interactions, what preemptive steps they are advising patients to take to protect themselves, and the pandemic’s impact in the oncology field.

Omid Hamid, MD
Chief, Translational Research and Immunotherapy
Director, Melanoma Therapeutics
The Angeles Clinic and Research Institute

I think the most important thing to note here is latency. If [COVID-19] is not an issue now, it will be soon and we must prepare ourselves, our clinics, and our patients for it. If you don’t believe this, just look at the initial cases reported in Japan 3 weeks ago and the follow-up. This will be the case in most places.

I tell my patients to limit nonessential [travel] and as for foreign travel—cancel. [Isolate yourself] if you have symptoms and minimize contact with others in a large setting. No handshakes, no hugs. Practice ENHANCED hygiene.

As [COVID-19] becomes more prevalent, our hospitals and emergency rooms will become flooded and access to care for our patients, whether for their cancer care or surgical/maternity care, will be compromised.

The real people in danger are those with comorbidities and pulmonary conditions. Think of them.

Hope S. Rugo, MD, FASCO
Director, Breast Oncology and Clinical Trials Education
The University of California, San Francisco Helen Diller Family Comprehensive Cancer Center

COVID-19 is the biggest medical issue we have faced in modern times and has had an impact on all aspects of society around the world. This novel viral infection is very communicable, and patients may be asymptomatic while communicable. The virus can live on surfaces for a long duration of time. Although the majority of deaths have occurred in elderly patients and those with underlying health issues, younger and healthy individuals have been very ill, requiring intensive support.

As the cases and deaths in Italy exploded over [the week of March 9], it became clear that the United States would not be far behind. The United States has had limited ability to test for the viral infection, which in turn markedly limits our ability to control spread of the infection. Finally, [the weekend of March 13], our local and national governments reacted to limit spread of the infection with strict guidelines for containment of populations. We don’t yet know if this will be enough and whether it was enacted soon enough.

In oncology, we are deluged now from 2 sides: our patients who are scared to come for treatment and scared to miss treatment, asking for guidance that we ourselves are learning along the way, and our institutions that are scrambling to create structures to protect staff and patients. We are screening all patients the day before their clinic appointments, and the viral pandemic has already led to much broader use of telemedicine, as we “see” our patients using videoconferencing to avoid exposing everyone to greater risk. It is clear that this [pandemic] will take a big toll on clinical research, as our coordinators are barred from patient areas, and in San Francisco, [they are barred] from coming in to work at all. The bottom line: [we must] protect our patients by canceling routine visits and imaging, [which allows] us to take the best care of those who need ongoing treatment. We need to all work a little harder, as efficiently as possible, and wash our hands!

For patients, there is still plenty of food and dry goods in the United States. Panic buying hurts everyone. Don’t come to clinic or go out if you have any viral symptoms, and get tested if you have a fever. There are guidelines online from the Centers for Disease Control that are updated regularly. For providers, the American Society of Clinical Oncology has guidelines specifically for oncology providers.

Debu Tripathy, MD
Chairman, Department of Breast Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

The impact of the rapid development of activities and events with the novel COVID-19 is unclear at this point. In our modern era, it is an interesting phenomenon to be involved in, in a virus that is a pandemic.

We’ve seen mini-pandemics with the Ebola virus. Ebola had a more virulent case fatality ratio but had very limited exposure. Now, COVID-19 does not have as high of a mortality rate but is so widespread. Currently, the mortality rate is estimated to be between 1% and 3%, which is, in orders of magnitude, higher than the flu.

There is much about COVID-19 that we don’t know yet. It appears that a group of asymptomatic patients can be carriers and contagious, which is concerning in terms of containment. Many countries and institutions are adopting different policies for containment.

[COVID-19] is fundamentally going to change the way we live our lives, at least in the short term. We don’t know which way this is going to move. I liken it to a tropical storm off the coast of Africa. Many storms begin there and mature into hurricanes as they move into the Western Hemisphere. They may wreak havoc, or they may move out to sea. The same happens with viral epidemics; there are so many factors that determine how they will operate.

REFERENCE
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Isatuximab Affords the R/R Multiple Myeloma Setting a Tolerable New Alternative

by RACHEL NAROZNIAK, MA

THE RECENT APPROVAL OF isatuximab-irfc (Sarclisa) combined with pomalidomide (Pomalyst) and dexamethasone offers adults with multiple myeloma whose disease has progressed after standard therapy a tolerable new treatment option.

On March 2, 2020, the FDA approved the triplet for adults with multiple myeloma who received ≥2 prior therapies including lenalidomide (Revlimid) and a proteasome inhibitor. The approval for the CD38-directed cytolytic antibody was based on efficacy results from the phase III ICARIA-MM (NCT02990338) trial, which showed that treatment with the triplet therapy conferred a significant survival benefit. The median progression-free survival (PFS) was 11.53 months with the regimen versus 6.47 months with pomalidomide and dexamethasone, translating to a greater than 40% reduction in the risk of disease progression or death (HR, 0.596; 95% CI, 0.44-0.81; \( P = .001 \)).

ICARIA-MM’s study population “represents a critical group of patients in multiple myeloma,” according to Ken Shain, MD, PhD, an assistant member of the departments of Malignant Hematology and Tumor Biology and the Chemical Biology and Molecular Medicine program at the Moffitt Cancer Center & Research Institute in Tampa, Florida. In an interview with OncologyLive®, Shain discussed isatuximab-irfc and its potential to move into different stages of the multiple myeloma paradigm following further clinical investigation.

Q How does the agent fit into the current treatment paradigm?

This is a question that we all will continue to strive to understand. We are always striving to improve our armamentarium; having more agents to control disease for longer periods is going to be important for our patients. I think isatuximab will initially be used primarily in later lines of therapy. Pomalidomide had been generally used in that setting but also has a critical role in combination with other CD38 antibodies earlier in therapy. That will create a space later in therapy to reuse this class of drugs in those 2 or 3 prior lines of therapy population.

Q What are the next steps for isatuximab-irfc?

Whenever we have a new agent approved, it allows us to start testing it with other drug combinations and in other disease settings. We will continue to ask questions and study its use in earlier relapse, maintenance therapy, and the newly diagnosed setting. Further, additional combination studies are being carried out and will continue to be carried out with other classes of drugs like PIs and selective nuclear export inhibitors. Answering these questions will provide our next steps.

A Tolerability is always critical, and so to get to a phase III study, isatuximab has gone through phase I trials, in which we have identified a tolerable dose, as well as a phase II study where an effective dose was selected. In the context of ICARIA-MM, isatuximab is a very well-tolerated drug, with the exception of infusion reactions. Approximately 38% of individuals experience an infusion reaction. Importantly, infusion reactions are expected with this class of agents and are generally relatively minor.

We also know that isatuximab will have some potential toxicities when given in combination with drugs like pomalidomide and dexamethasone. Isatuximab is very well-tolerated therapy that did not add significant toxicities to pomalidomide and dexamethasone outside of infusion reactions. Regardless, it is critical for us to be mindful of toxicities and carefully monitor our individual patients because they may experience some additional toxicities.

Q What do we know about the agent’s tolerability?

In a disease like myeloma that we cannot control forever, we need to continue to develop new drugs and drug combinations to maintain control of the disease so that our patients can live as long as possible. In this randomized phase III study, relapsed and refractory patients, defined by having received and failed 2 or more prior lines of therapy containing both lenalidomide and a proteasome inhibitor (PI), were enrolled. To this end, the study population represents a critical group of patients in multiple myeloma.

Q What is the agent’s mechanism of action?

Isatuximab is a monoclonal antibody that targets a protein called CD38 on the surface of multiple myeloma cells. Importantly, myeloma cells express this protein more than any other cell in the body, so it has become a very exciting target with an excellent therapeutic index in multiple myeloma. We have learned, both from isatuximab and from daratumumab [Darzalex], that targeting CD38 in myeloma is very effective in attacking myeloma cells.

Isatuximab targets and kills myeloma cells in a number of ways, including directly via apoptosis, which appears to be unique to isatuximab as a CD38-targeting agent, and indirectly through antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis. It may also function in an additional immunomodulatory capacity. Thus, isatuximab has a multifaceted way of helping us attack myeloma cells. This is likely why it works well in combination with other agents such as pomalidomide and dexamethasone.

Q What do we know about the agent’s tolerability?

T tolerability is always critical, and so to get to a phase III study, isatuximab is very well-tolerated therapy. The triplet regimen provides an effective therapy that we can use to help our patients achieve a good median survival.

ICARIA-MM’s study population “represents a critical group of patients in multiple myeloma,” according to Ken Shain, MD, PhD, an assistant member of the departments of Malignant Hematology and Tumor Biology and the Chemical Biology and Molecular Medicine program at the Moffitt Cancer Center & Research Institute in Tampa, Florida. In an interview with OncologyLive®, Shain discussed isatuximab-irfc and its potential to move into different stages of the multiple myeloma paradigm following further clinical investigation.

REFERENCE

FDA APPROVAL—March 2, 2020

FDA grants approval for the CD38-directed monoclonal antibody isatuximab-irfc in combination with pomalidomide (Pomalyst) and dexamethasone in adults with multiple myeloma who have received ≥2 prior therapies including lenalidomide (Revlimid) and a proteasome inhibitor.

Mechanism of action:
- Binds to CD38 expressed on tumor cells, including multiple myeloma cells, and inhibits the ADP-riboseyl cyclase activity of CD38
- Can activate natural killer cells when CD38-positive target tumor cells are not present and is able to suppress CD38-positive T-regulatory cells
- Induces apoptosis of malignant cells
- Activates immune effector mechanisms such as antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity

How supplied:
- 10 mg/kg given as an intravenous fusion every 2 weeks for 4 weeks and then every 2 weeks in combination with pomalidomide and dexamethasone until disease progression or unacceptable toxicity
- Premedicate with dexamethasone, acetaminophen, H2 antagonists, and diphenhydramine.

Company: Sanofi-Aventis US, LLC

PIVOTAL EFFICACY DATA FOR APPROVAL

ICARIA-MM (NCT02990338)—a multicenter, double-arm, phase III trial, that enrolled 307 patients with relapsed/refractory multiple myeloma who had received ≥2 prior therapies including lenalidomide and a proteasome inhibitor

Efficacy Results in the ICARIA-MM Study

Outcome | Isa-Pd (n = 154) | Pd (n = 153) |
--- | --- | --- |
ORR (95% CI) | 60.4 (52.5%-68.2%) | 35.3 (27.8%-43.4%) |
Stringent complete response + complete response | 4.5% | 2% |
Very good partial response | 27.3% | 6.5% |
Partial response | 28.6% | 26.8% |
Median progression-free survival (95% CI; months) | 11.53 (8.94-13.9) | 6.47 (4.47-8.28) |
HR (95% CI) | 0.596 (0.44-0.81) |

Isa-Pd indicates isatuximab-irfc, pomalidomide, and dexamethasone; ORR, overall response rate; Pd, pomalidomide and dexamethasone.

Other Warnings and Precautions
- Infusion-related reactions: Interrupt isatuximab-irfc and manage appropriately. Permanently discontinue for grade ≥3 reactions.
- Neutropenia: Monitor complete blood cell counts and observe patients for signs of infection. Dose delays and a colony-stimulating factor may be necessary to improve neutrophil count.
- Second primary malignancy: Monitor patients for development of second primary malignancies, per International Myeloma Working Group guidelines.
- Embryo-fetal toxicity: Exposure to isatuximab-irfc can cause fetal harm.

Commonly reported adverse events in ICARIA-MM study

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Isa-Pd (n = 152)</th>
<th>Pd (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>57%</td>
<td>9.0%</td>
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<tr>
<td>Infusion-related infection</td>
<td>38%</td>
<td>2.6%</td>
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<tr>
<td>Pneumonia</td>
<td>31%</td>
<td>25.3%</td>
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<tr>
<td>Diarrhea</td>
<td>26%</td>
<td>2.0%</td>
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<tr>
<td>Dyspnea</td>
<td>17%</td>
<td>5%</td>
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<tr>
<td>Nausea</td>
<td>15%</td>
<td>0%</td>
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<tr>
<td>Febrile neutropenia</td>
<td>12%</td>
<td>12.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Isa-Pd indicates isatuximab-irfc, pomalidomide, and dexamethasone; Pd, pomalidomide and dexamethasone.

References
INTERACTIVE NEWS

A selection of exclusive articles and videos available on OncLive.com and other MJH Life Sciences™ websites.

TOP TWEETS

@OncLive
Despite a decrease in gastric cancer and CRC diagnoses in the overall population, there has been an “alarming” rise in the incidence of these malignancies in young adults #crcsm #gicsm @cityofhope onclive.com/link/7437

@OncLive
Infectious diseases are the second leading cause of mortality in patients with cancer, whose immune systems are often compromised, so it is essential for providers to keep up with developments in the management of #coronavirus disease 2019 #COVID-19. Telemedicine systems can be used to prevent overcrowding and limit human exposure to COVID-19 while continuing to facilitate high-quality care.

ONCLIVE® VIDEOS

OH ON REMAINING CHALLENGES IN PROSTATE CANCER
Although new therapies have become available for use in earlier lines of prostate cancer, they are not curative and result in ambiguity on how to best treat patients when they eventually relapse, according to William K. Oh, MD, chief, Division of Hematology and Medical Oncology, Mount Sinai Health System and deputy director, The Tisch Cancer Institute.

SNYDER ON TRANSPLANT UPDATES IN MYELOFIBROSIS
Reduced-intensity conditioning regimens have made transplant safer for older patients with comorbidities, says David S. Snyder, MD, associate chair, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, who added that now, physiologic age rather than chronologic age is what determines patient eligibility for transplant.
KTE-X19 Poised to Have a Promising Future in the MCL Paradigm

Interview with David Miklos, MD

As the investigational CAR T-cell therapy KTE-X19 awaits FDA approval as a treatment for patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL), additional follow-up and analyses will determine the durability of responses the agent has elicited in patients and how it will best fit into the paradigm.

In February 2020, the FDA granted a priority review designation to a biologics license application for KTE-X19 in this setting, based on data from the phase II ZUMA-2 trial (NCT02601313). At a median follow-up of 12.3 months, results showed that KTE-X19 demonstrated an objective response rate of 93% in patients with RR MCL. A complete response rate of 67% was also observed.

“We will need additional long-term follow-up to determine the durability of these responses, but [the fact that] 50% of patients are achieving durability is very promising,” said Miklos, an author of the ZUMA-2 trial. “The publications are under way, and the package [for approval of this therapy] has been submitted to the FDA.”

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Notable Quotables

“CAR T cells are here to stay. We now know that the technology works, and we hope that it is going to cure a large proportion of patients.”

—Dimitrios Tzachanis, MD, PhD
Assistant professor of medicine at University of California, San Diego Health

“Cancer centers should take the initiative to offer guidelines [on coronavirus disease 2019] to our patients and ensure that they are disseminated throughout the clinics.”

—Nabil F. Saba, MD, FACP
Director of the Head and Neck Medical Oncology Program at the Winship Cancer Institute of Emory University

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Spotlight

Brahmer on Driver Mutations in NSCLC

Advances in non–small cell lung cancer have led to the development of several targeted agents for patients with driver mutations, according to Julie R. Brahmer, MD, codirector of the Upper Aerodigestive Department in the Bloomberg-Kimmel Institute for Cancer Immunotherapy. These options include osimertinib (Tagrisso) and alectinib (Alecensa), among others.

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Hamid on Biomarker of Response to Docetaxel in mHSPC

Data from the phase III CHAARTED trial (NCT00309985) suggest that the luminal B subtype may predict response to docetaxel in patients with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC), said Anis Hamid, MBBS, genitourinary oncology research fellow, Dana-Farber Cancer Institute.

READ MORE onclive.com/link/7435

Have you been to an OncLive® State of the Science Summit™? Tag us in one of your photos on social media and we might feature it in an upcoming publication! Find us on Twitter at @OncLive and @OneLiveSOSS, as well as on Facebook at OncLive and OncLive State of the Science Summit.
~40% of patients with advanced HCC are AFP-High (AFP ≥ 400 ng/mL)\(^1-3\)

References

AFP=alpha-fetoprotein; HCC=hepatocellular carcinoma.
What can that mean for their prognoses?

Learn more at www.AFPHpatientpop.com
RESULTS FROM THE FIRST FDA-approved in-human trial of CRISPR-edited T cells for cancer treatment suggest that such therapies can be used safely in patients, allaying some of the concerns about potential adverse effects (AEs) from the gene-editing tool and advancing progress toward the development of more effective cell-based immunotherapies.1

Investigators who led the trial at the University of Pennsylvania’s Abramson Cancer Center in Philadelphia (UPenn) for patients with refractory cancers are planning a follow-up safety study that will increase the dose of engineered T cells and target a different protein with the goal of boosting efficacy. Several other academic and industry groups in the United States are preparing similar studies and several such trials are under way in China.

The technology is also being used to build a map of cancer gene targets and biologists are creating tissue models to test for AEs associated with CRISPR editing.

Additionally, investigators are employing the technique to explore treatments for sickle cell anemia and other diseases, including coronavirus disease 2019 (COVID-19). In mid-March, as the pandemic worsened in the United States, scientists from the New York Genome Center in New York, New York, reported that CRISPR-based genetic screens can be used to identify potential predictive and therapeutic targets for COVID-19.2

CRISPR, which refers to clustered regularly interspaced short palindromic repeats, are genomic sequences bacteria use to recognize and destroy foreign DNA through an enzyme, frequently CRISPR-associated (Cas) protein Cas9, guided by an RNA molecule (FIGURE). This approach enables gene editing that is much faster, less expensive, and more specific than prior methods.3

The positive findings from the UPenn team were announced in February amid heightened concern in the global research community over potential misuse of CRISPR. In December 2019, a Chinese court sentenced scientist He Jiankui to 3 years in prison for misconduct related to a CRISPR experiment that modified the germline in human embryos to confer resistance to HIV.4 His work, which reportedly resulted in the births of 3 genetically engineered babies, was widely condemned for violating ethical norms and taking unnecessary risks.

The UPenn trial and other proposed studies of CRISPR-modified T cells differ significantly from He’s experiment: the oncology research does not involve embryos, it targets somatic rather than germline cells, and the CRISPR/Cas9 editing tool is currently used ex vivo to modify cells in a lab, rather than being injected into patients to change DNA in the body. The UPenn study also underwent an ethics review and a lengthy FDA approval process.

Concerns for patients in the T-cell study include immune reactions to the Cas9 protein and off-target edits that may create unsafe chromosomal rearrangements, such as changes that cause T-cell lymphoma. Although every T-cell therapy with a different set of edits will have to be checked again, the UPenn investigators have so far found no such AEs, said Jennifer R. Hamilton, PhD, a postdoctoral fellow at the Doudna Lab at the University of California Berkeley.

“Continuing to look at safety will be important. It’s really early days in being able to do these studies,” said Hamilton, who coauthored a Science perspective on the trial with CRISPR pioneer Jennifer Doudna, PhD.5 That said, she added, “It’s a really exciting time for gene editing and engineered cells. A lot of what we figured out in the gene editing field can enable better anticancer engineered cell therapeutics.”

Engineered T cells created with editing tools like CRISPR may eventually be able to treat patients with metastatic cancers that cannot be managed with existing immunotherapies alone, said Carl H. June, MD, a coauthor of the UPenn T-cell study. June is the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine and director of the Center for Cellular Immunotherapies, both at Penn Medicine. In 2015, he was named a Giants of Cancer Care® award winner for his work with chimeric antigen receptor (CAR) T-cell therapy in patients with leukemia and lymphoma.

“Synthetic biology offers the ability to make cells much more potent than the way we’re born with. That’s what our goal was here,” June said. “It will work hand in hand, I think, with things like checkpoint therapies and vaccines.”
NOVEL THERAPY IS FEASIBLE

The phase 1 trial (NCT03399448) was designed to assess the safety and feasibility of infusing autologous cancer/testis antigen 1 (NY-ESO-1) T-cell receptor (TCR)-engineered T cells, called NYCE cells, in patients after CRISPR/Cas9 editing of the TRAC-α (TRAC), TCR-β (TRBC), and PDCD1 loci. The trial used a TCR rather than a CAR to reduce the incidence of cytokine release syndrome associated with CAR T-cell therapy and allow better assessment of potential AEs from CRISPR/Cas9 editing.

“The ‘feasible’ aspect comes in because it’s the most complex cell manufacturing we’ve ever done, and the patients were really beat up—in the case of 1 patient, 8 different lines of chemotherapy and 3 different bone marrow transplants,” June said. “So you don’t necessarily know if their cells will still grow.”

The trial team enrolled 6 patients, harvested T cells from 4 of them, and used CRISPR to knock out PDCD1, which encodes the PD-1 immune checkpoint, and 2 endogenous TCR domain genes, TRAC and TRBC. The endogenous TCRs were removed to prevent mispairing and competition for expression with the synthetic TCR, increasing the effectiveness of the therapy and preventing autoimmune effects that have been seen in animal studies, June said. Disrupting PD-1 has been shown to improve T-cell killing of tumor cells. The cells were then transduced with a lentiviral vector to express a transgenic TCR for NY-ESO-1, a cancer/testis antigen.

One patient progressed during the cell-preparation process and entered hospice. The NYCE cells were reinfused in the 3 other patients: 2 with refractory advanced myeloma and 1 with a refractory metastatic sarcoma not responding to multiple prior therapies. The patients were given lymphodepleting chemotherapy with cyclophosphamide and fludarabine on days 3 and 5 prior to T-cell administration and a single infusion of 1 × 10^6 manufactured engineered T cells per kilogram.

The transduced cells persisted in the blood for up to 9 months after infusion, far longer than previously reported trials with NY-ESO-1–engineered T cells, which had half-lives in the blood of about 1 week, the investigators said. No patient experienced cytokine release syndrome or overt AEs attributed to the cell infusion.

The best clinical responses were stable disease in 2 patients. One had a mixed response with an approximately 50% decrease in a large abdominal mass that persisted for 4 months, although other lesions progressed. As of December 2019, all patients had experienced disease progression, with 2 receiving other therapies and 1 dying from myeloma.

Engineered T cells taken from the blood at 9 months continued to exhibit anticancer activity in lab tests. The NYCE cells were also present in tumor and blood marrow biopsies but their level of functioning there is unknown, June said.

One potential pitfall of gene editing is that it may result in unintended chromosomal deletions and rearrangements, investigators have noted in preclinical findings. CRISPR/Cas9 works by causing DNA double-strand breaks, and the Cas9 “molecular scissors” protein can end up cutting in the wrong place. After an on-target cut, the natural DNA repair process that completes an edit can also result in the end of a chromosome, creating a translocation.

UPenn investigators assayed for 12 potential translocations, finding them in progressively declining numbers during the T-cell manufacturing process and after reinfusion. The falling frequency of these rearrangements suggests that “they conferred no evidence of a growth advantage over many generations of expansion in the patients’ and thus no sign of oncogenicity, study authors wrote.

“T cells are pretty fault-tolerant. You can kind of have mayhem happen on them and they don’t turn into cancer. If you do it to your bone marrow stem cells, you’re much more likely to get a leukemia or some other kind of cancer,” June said.

Cas9 is derived from Streptococcus pyogenes, which causes strep throat and other infections. The protein provokes an immune response in healthy people that could destroy engineered T cells. However, testing of the 3 patients did not show any such responses, which the investigators said could be a result of the small amount of Cas9 in the engineered T-cell product or immunodeficiency in patients with extensive previous treatment histories.

Hamilton attributed the absence of unwanted responses to the method by which the editing complex was inserted into the T cells. Investigators used a 2-step process, first knocking out the 3 genes with electroporation of ribonucleoprotein (RNP) complexes comprising recombinant Cas9 and then transducing the cells with a viral vector to express TCR, which in turn, recognizes NY-ESO-1. The Cas9 was not integrated into the cell DNA and was
not replicated, and the protein degraded to below-detectable levels before reinfusion, she said.

**NEXT STOP: CARS**

June said his group’s next trial will aim for greater efficacy by using a CAR rather than a TCR, switching to CD19 as the target, and giving multiple infusions of engineered T cells at higher doses. It will also use more advanced cell culture reagents than were available when the NY-ESO-1 study protocols were established several years ago, which will enable higher levels of editing. Although the completed trial knocked out 15% to 45% of the target genes at the 3 loci, newer methods allow greater than 90% on-target editing of T-cell DNA, June said.

Intensifying the therapy may increase the number of chromosomal translocations, but that is not a major concern if the gene editing still avoids creating highly proliferative mutant cells, Hamilton noted.

Investigators at Memorial Sloan Kettering Cancer Center in New York have proposed a similar trial that could further boost the effectiveness of engineered T cells by more precisely inserting a CD19-directed CAR. Rather than using a lentivirus to infect the T cell and place the CAR randomly into the DNA, the alternative method uses CRISPR to knockout the native TRAC gene and an adeno-associated virus to place the CAR there. In a mouse study, the TRAC-CAR cells were more durable and demonstrated superior antitumor activity than conventional CAR T cells.7 In another preclinical study, investigators dispensed with viruses entirely, electropropating a linear piece of DNA into cells along with Cas9 RNPs.8 Several other in-human trials of CRISPR-engineered T cells to treat cancer are under way. CRISPR Therapeutics, a Cambridge, Massachusetts-based firm cofounded by CRISPR pioneer Emmanuelle Charpentier, PhD, is treating patients in 2 trials evaluating allogeneic CRISPR/Cas9 gene-edited CAR T-cell therapies.9 A phase I/II study (NCT04035434) of the CD19-directed therapy CTX110 aims to recruit 95 patients with relapsed or refractory B-cell malignancies and non-Hodgkin lymphoma (NHL). A phase 1 study (NCT04244656) of the anti-BCMA agent CTX120 is enrolling up to 80 patients with relapsed or refractory multiple myeloma.

The company is also planning a trial of CTX130, a CAR T-cell therapy targeting CD70 for the treatment of solid tumors and hematologic malignancies, and has active trials of a hematopoietic stem cell therapy for sickle cell disease (NCT03745287) and transfusion-dependent β-thalassemia (NCT03655678). Its research areas include a treatment for type 1 diabetes and in vivo CRISPR-based therapies for cystic fibrosis and other rare genetic diseases.

Intellia Therapeutics, also based in Cambridge, is planning a trial next year of NTLA-5001, a CRISPR-engineered autologous T-cell therapy directed toward Wilms tumor 1 antigen, an overexpressed protein associated with acute myeloid leukemia.10 The company is working on a sickle cell treatment as well as in vivo therapies for hereditary angioedema and for transthyretin amyloidosis, a protein misfolding disorder that affects the heart and nerves. Other pending trials include one recently posted by the Center for Cell and Gene Therapy at Baylor College of Medicine in Houston, Texas. The phase I study (NCT03690011), which is not yet recruiting, will evaluate a CRISPR-edited, CD7-directed CAR therapy with added CD28 to treat patients with T-cell acute lymphoblastic leukemia or lymphoma or NHL, according to the ClinicalTrials.gov website. Several other US companies and academic institutions are researching CRISPR-based cancer therapies but have not yet reached the clinical trial stage.

**USES FOR CRISPR EXPAND**

Although the UPenn findings mark a milestone for CRISPR research in the United States, Chinese investigators have been testing the technology for several years. The first-ever in-human use of a CRISPR-based therapy occurred in 2016, when Chinese researchers knocked out the PD-1 gene on T cells to treat a patient with metastatic non-small cell lung cancer.11,12 There are currently at least 10 trials of CRISPR-based therapies in China, targeting mesothelin-positive solid tumors, CD19-positive leukemia or lymphoma, esophageal cancer, Epstein Barr virus–associated malignancies, HIV in patients with cancer, and other conditions such as pulmonary tuberculosis and sepsis, according to a search of ClinicalTrials.gov.

Meanwhile, in vivo use of CRISPR in humans, in which a full gene editing construct is injected into the body to modify somatic DNA, is just getting started. The first in vivo CRISPR-based clinical trial (NCT03872479), launched last year by Allergan and Editas Medicine, seeks to evaluate AGN-151587 (EDIT-101) in patients with Leber congenital amaurosis 10, a rare type of blindness caused by a genetic mutation. Labs around the world are conducting preclinical work on in vivo CRISPR therapies for cancer and many other diseases. June said it may take another decade of research before such therapies are feasible.

“The issue there is the efficiency of it and making sure it’s safe and doesn’t go germ-line, meaning it doesn’t go into sperm or eggs,” he said. “There are a lot of technical challenges, but the field’s been advancing very rapidly.”

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**“It’s a really exciting time for gene editing and engineered cells. A lot of what we figured out in the gene editing field can enable better anticancer engineered cell therapeutics.”**

—JENNIFER R. HAMILTON, PHD

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CRISPR is also being used to facilitate development of cancer therapies and highly targeted precision medicine. The Broad Institute of MIT and Harvard is using CRISPR and other technologies to create a Cancer Dependency Map that profiles cancer cell line models for genomic information and sensitivity to genetic and small molecule perturbations.

CRISPR loss-of-function screens are used to knock out thousands of different genes in cell lines and measure which deletions lead to cell death, allowing investigators to determine which genes are essential for each cancer type and link them to tumor genetic or molecular features, said Jesse Boehm, PhD, scientific director of the Cancer Dependency Map and associate director of the Broad Cancer Model Development Center.

New data sets are regularly published on an open-access website, Depmap.org. Broad scientists have identified about 500 strong cancer targets, including 150 that may be targetable with existing drugs, and they have so far attempted to confirm 25 of those links through preclinical analyses, Boehm said.

In a study published last year, investigators used CRISPR and other technologies to screen for potential targets against malignant rhabdoid tumors (MRTs), which are aggressive cancers of the kidney, brain, and soft tissues that usually affect young children. They identified MDM2 and MDM4, canonical negative regulators of the tumor suppressor p53, as valid targets. They then demonstrated that 2 investigational drugs, idasanutlin (MDM2-specific) and ATSP-7041 (MDM2/4-dual) caused MRT regression in mice.13

Investigators and colleagues at the Broad Institute also used CRISPR screening data to identify WRN, which encodes a DNA helicase, as a synthetic lethal target in microsatellite unstable cancers, setting the stage for drug company research on compounds that can be combined with checkpoint inhibitors to treat colorectal tumors and other cancers.14

Boehm said his group would like to see their findings eventually inform therapeutic decision making in a manner similar to the way research has elucidated clinical pathways.

“Ten years from now, we do aspire for the Dependency Map to be something that oncologists use to prescribe the right drug to the right patient, essentially achieving the promise of precision medicine,” he said. In the longer term, it may become possible to screen individual patient tumor tissue samples using CRISPR-based methods to determine the most effective therapy, Boehm added.

Another research effort seeks to better understand the variety of potential AEs from gene editing. With funding from the National Institutes of Health (NIH) Common Fund’s Somatic Cell Genome Editing program, investigators are studying human tissue models, delivery methods, reporter systems, and other technologies that facilitate testing of the effects of CRISPR/Cas9. Different groups in the NIH consortium are working with animal models, brain organoids, and T cells, among other systems.

Todd McDevitt, PhD, a senior investigator at Gladstone Institutes in San Francisco, California, is working on creating tissues from human stem cells to use as a substrate for testing CRISPR and other tools. McDevitt said in an interview that he is interested in knowing whether a certain volume of Cas9 proteins will cause cells to malfunction, for example, by disrupting ion regulation in cardiac tissue and affecting the heartbeat. Some of the potential effects cannot be tested in animal models, he said.

“Those are too different, so that’s why we’re trying to use some of the human models for those kinds of questions,” said McDevitt, who also is a professor of bioengineering at the University of California San Francisco. “Ultimately, a new product would have to go through several of these kinds of things in different systems to really test the effects well.”
CONTRAINDICATIONS
DARZALEX® (daratumumab) is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation.

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

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

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

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

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

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

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

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

Learn more at darzalexhcp.com

References:
1. Biotech, Inc.

[Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.
DARZALEX® (daratumumab) + Rd*

REDEFINING APPROACHES IN TRANSPLANT-INELIGIBLE, NEWLY DIAGNOSED MULTIPLE MYELOMA

For a strong start to their treatment journey

*Rd=lenalidomide (R) + dexamethasone (d).

 Longer PFS and deep responses

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

 Demonstrated safety profile when combined with Rd in the MAIA study2

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

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

DARZALEX® is a CD38-directed cytolytic antibody indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy


Please see Important Safety Information and Brief Summary of full Prescribing Information on adjacent pages.

Learn more at darzalexhcp.com

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DARZALEX® (daratumumab) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion Reactions: DARZALEX can cause severe and/or serious infusion reactions including anaphylactic reactions. In clinical trials, approximately half of 8 patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and gave Grade 1-2 [see Adverse Reactions]. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypotension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and anemia. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritis, and hypotension [see Adverse Reactions].

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,686 patients with multiple myeloma including 1,910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant Combination Treatment with Lenalidomide and Dexamethasone (RDd)

Adverse reactions described in the table below reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range 0.1 to 40.44 months) for the daratumumab–lenalidomide–dexamethasone (RDd) group and median treatment duration of 21.3 months (range: 0.03 to 40.64 months) for the lenalidomide–dexamethasone group (Rd) in a Phase 3 active-controlled study MAIA. The most frequent (≥20%) adverse reactions were infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea and cough. Serious adverse reactions with a 2% greater incidence in the RDd arm compared to the Rd arm were pneumonia (RDd 15% vs Rd 8%), bronchitis (RDd 4% vs Rd 2%) and dehydration (RDd 2% vs Rd <1%).

Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the RDd Arm and MAIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RDd (N=364)</th>
<th>Rd (N=365)</th>
<th></th>
<th>RDd (N=365)</th>
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<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
<td>Any Grade (%)</td>
</tr>
<tr>
<td>Infusion reactions*</td>
<td>61 2</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<td>Diarrhea</td>
<td>57 7</td>
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<td>General disorders and administration site conditions</td>
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<td>Peripheral edema*</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>32 3</td>
<td>&lt;1</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Cough*</td>
<td>30 1</td>
<td>&lt;1</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>13 6</td>
<td>&lt;1</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
DARZALEX® (daratumumab) injection

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

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

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>D-VMP (N=346) %</th>
<th>VMP (N=354) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>(%</td>
<td>(%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>84</td>
<td>41</td>
</tr>
</tbody>
</table>

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

Combination Treatment with Bortezomib, Melphalan and Prednisone

Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 14.7 months (range: 0 to 25.8 months) for the daratumumab, bortezomib, melphalan and prednisone (D-VMP) group, and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in a Phase 3 active-controlled study ALCYONE. The most frequent adverse reactions (>20% with at least 5% greater frequency in the D-VMP arm) were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the D-VMP Arm in ALCYONE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>D-VMP (N=346) %</th>
<th>VMP (N=354) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Infusion reactionsa</td>
<td>28</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Edema peripheralb</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infectionc</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Pneumoniaa</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cougha</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertensiona</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

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

Combination Treatment with Bortezomib, Thalidomide and Dexamethasone

Adverse reactions described in Table 5 reflect exposure to DARZALEX up to day 100 post-transplant in a Phase 3 active-controlled study CASSIOPEIA (see Clinical Studies (14.1) in Full Prescribing Information). The median duration of induction/ASCT/consolidation treatment was 8.9 months (range: 7.0 to 12.0 months) for the DTd group and 8.7 months (range: 6.4 to 11.5 months) for the VTd group. The most frequent adverse reactions (>20% with at least 5% greater frequency in the DTd group) were infusion reactions, nausea, pyrexia, upper respiratory tract infection and bronchitis. Serious adverse reactions with a 2% greater incidence in the DTd arm compared to the VTd arm were bronchitis (DTd 2% vs VTd <1%) and pneumonia (DTd 8% vs VTd 4%).

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in CASSIOPEIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=364) %</th>
<th>% Rd (N=365) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>48</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>88</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>86</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>85</td>
<td>46</td>
<td>12</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

Newly Diagnosed Multiple Myeloma Eligible for Autologous Stem Cell Transplant Combination Treatment with Bortezomib, Thalidomide and Dexamethasone (DTd)

Adverse reactions described in Table 5 reflect exposure to DARZALEX for a median treatment duration of 14.7 months (range: 0 to 25.8 months) for the daratumumab, bortezomib, melphalan and prednisone (D-VMP) group, and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in a Phase 3 active-controlled study ALCYONE. The most frequent adverse reactions (>20% with at least 5% greater frequency in the D-VMP arm) were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 5: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the D-VMP Arm in CASSIOPEIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DVTd (N=536) %</th>
<th>VTd (N=538) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Infusion reactionsa</td>
<td>35</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infectiona</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cougha</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertensiona</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>
**DARZALEX** (daratumumab) injection

Combination Treatment with Lenalidomide and Dexamethasone

Adverse reactions described in Table 7 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for the daratumumab-lenalidomide-dexamethasone (DRd) group and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide-dexamethasone (Rd) group in a Phase 3 active-controlled study POLLUX. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 47% for the Rd group. Serious adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Adverse reactions described in Table 9 reflect exposure to DARZALEX for a median treatment duration of 6.5 months (range: 0 to 14.8 months) in the daratumumab-bortezomib-dexamethasone (DVd) group and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib-dexamethasone (Vd) group in a Phase 3 active-controlled study CASTOR. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, rhinitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
d

### Table 6: Treatment-Emergent Hematology Laboratory Abnormalities in CASSIOPEIA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DVd (N=536) %</th>
<th>Vd (N=538) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 7: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=283) %</th>
<th>Rd (N=281) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243) %</th>
<th>Vd (N=237) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 8: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DRd (N=283) %</th>
<th>Rd (N=281) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

### Table 9: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DVd Arm CASTOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243) %</th>
<th>Vd (N=237) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
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<tr>
<td>Muscle spasms</td>
<td></td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

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

** Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.
**DARZALEX® (daratumumab) injection**

- Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.
- edema peripheral, edema, generalized edema, peripheral swelling
- upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metagenome virus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection, bronchitis, bacterial, epiglotitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
- cough, productive cough, allergic cough
- dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 10.

### Table 10: Treatment-Emergent Hematology Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>48</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>90</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>89</td>
<td>41</td>
<td>7</td>
</tr>
</tbody>
</table>

Key: D=Daratumumab, Vd=voretizomib-dexamethasone.

Combination Treatment with Pomalidomide and Dexamethasone
Adverse reactions described in Table 11 reflect exposure to DARZALEX, pomalidomide and dexamethasone (DPd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months) in EQUULEUS. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, back pain, arthralgia, dizziness, insomnia, cough and dyspnea. The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations for 13% of patients.

### Table 11: Adverse Reactions With Incidence ≥10% Reported in EQUULEUS

<table>
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<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
<td>50</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea 38</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation 33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Nausea 30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting 21</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
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<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue 50</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pyrexia 25</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Chills 20</td>
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<td></td>
<td>Edema peripheral 17</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Acrinia 15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Non-cardiac chest pain 15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pain 11</td>
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<td>0</td>
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</tbody>
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<table>
<thead>
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<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection 50</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pneumonia 15</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
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<th>Body System</th>
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<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalemia 16</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia 13</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite 11</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 12: Treatment-Emergent Hematology Laboratory Abnormalities in EQUULEUS

<table>
<thead>
<tr>
<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>57</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>95</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>94</td>
<td>45</td>
<td>26</td>
</tr>
</tbody>
</table>

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

### Table 13: Adverse Reactions With Incidence ≥10% in Patients With Multiple Myeloma Treated With DARZALEX 16 mg/kg

<table>
<thead>
<tr>
<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
<td>48</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue 39</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pyrexia 21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Chills 10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Monotherapy
The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 13. Table 14 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

### Table 14: Grade 3–4 Laboratory Abnormalities Reported at a Rate of ≥10% in EQUULEUS

<table>
<thead>
<tr>
<th>Body System</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
<td>48</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
The incidence of infusion modification due to reactions was 36%. Median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours).

Grade 3/4 infusion reaction at Week 2 or subsequent infusions. Less than 1% of patients had a cumulative 6% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

In EQUULEUS, patients receiving daratumumab combination treatment (n=97) re-initiation of DARZALEX following ASCT were consistent in terms indicated population is unknown. All pregnancies have a background risk of any remaining endogenous M protein in the patient's serum, to facilitate approval daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein. False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

**DRUG INTERACTIONS**

**Effects of Daratumumab on Laboratory Tests:** Interference with Indirect Antiglobulin Tests (Direct Coombs Test). Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interferes with standard amboceptor tests used to detect DTT sensitive Kell-positive units. Daratumumab is also sensitive to DTT treatment, K-negative units should be supplied after treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

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

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy: Risk Summary:** There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations (see Clinical Considerations). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

---

**Table 13: Adverse Reactions With Incidence ≥10% in Patients With Multiple Myeloma Treated With DARZALEX 16 mg/kg (continued)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>23</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia a</td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 14: Treatment-Emergent Grade 3-4 Laboratory Abnormalities (≥10%)**

<table>
<thead>
<tr>
<th>Daratumumab 16 mg/kg (N=156)</th>
<th>Any Grade (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>45</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>48</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>72</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

**Notes:**

- a Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.
- b Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.
DARZALEX® (daratumumab) injection

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

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

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

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

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

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

Geriatric Use: Of the 2,066 patients that received DARZALEX at the recommended dose, 37% were 65 to 75 years of age, and 16% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients [see Clinical Studies (14) in Full Prescribing Information].

REFERENCES

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

Infusion Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:
• itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see Warnings and Precautions and Adverse Reactions].

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

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

Interference with Laboratory Tests
Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions and Drug Interactions].

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

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Pivotal Studies Provide New Path in Smoldering Myeloma

by SAGAR LONIAL, MD

THE DIAGNOSIS AND MANAGEMENT of smoldering multiple myeloma (SMM) is an area of tremendous focused research and change over the past decade, with trials yielding intriguing findings that have the potential to change practice.

Prior to this breakthrough research, studies in the area were limited by 2 major issues: limited methods for risk stratifying this very heterogeneous group of patients defined as having SMM, and treatment that was mostly dependent upon the use of alkylator- and steroid-based approaches. A trial using thalidomide (Thalomid) in an unselected group of patients with SMM demonstrated that although there were responses, those who did respond actually had a shorter time to develop multiple myeloma (MM) than those who did not respond, resulting in the abandonment of this treatment approach.

This all changed dramatically in 2013 when the Spanish Myeloma Group presented and published their landmark trial evaluating the use of lenalidomide (Revlimid) plus dexamethasone versus observation in a large randomized clinical trial among a group of patients with high-risk SMM using a new approach to risk stratification. The trial demonstrated significant improvement in time to developing myeloma and overall survival (OS) favoring the use of early therapy. Over the intervening 7 years, many groups embarked on different approaches to early intervention in SMM, ranging from low-intensity therapy with single agents or doublets all the way to full myeloma-like therapy with triplet induction, transplant, and triplet consolidation. Each of these trials has demonstrated varying levels of efficacy, minimum residual disease (MRD) negativity, and overall response rate, but has been limited by short-term follow-up and not using a uniform method for assessing who fits into the high-risk category.

At the same time, many groups were working on revised risk-assessment methods. In 2018, the group from Mayo Clinic published their 20/20/20 criteria, which is very easy to use from a routine testing aspect and is very effective at risk stratification for patients seen in routine practice. This has now become more standard methodology that is currently being used for trials.

Recently, results from the E3A06 trial (NCT01169337) were published in the Journal of Clinical Oncology. The study, which is the largest randomized trial in the setting of SMM, randomized patients to either lenalidomide or observation. No dexamethasone was used as part of this trial to try and isolate the effect of lenalidomide. More importantly, all patients underwent screening of the spine and a pelvic MRI before study entry to reduce the risk of patients with MM being enrolled, as was the concern for the Spanish trial above.

The results of E3A06 demonstrated significant improvement in time to develop myeloma for the group randomized to lenalidomide, with an effect size of similar magnitude to that seen with the Spanish trial. With a 36-month follow-up, there was no difference in OS. A subset analysis using the highest-risk group of the Mayo 2018 criteria showed a 90% reduction in the risk of progression at 3 years for the group who received early lenalidomide. This led the authors to conclude that for the highest-risk group, early therapy should be considered using lenalidomide or lenalidomide/dexamethasone for patients who are not enrolling on a clinical trial.

At the same time, data from the next Spanish trial, GEM-CESAR (NCT02415413), were presented using the more intensive approach of induction with lenalidomide plus carfilzomib (Kyprolis) and dexamethasone (KRd), transplant, and KRd consolidation followed by...
lenalidomide maintenance. This trial demonstrated high frequency of MRD negativity that increased over time, but at 3 years, the progression-free survival was similar to that demonstrated in E3A06, at 92% with intensive therapy versus 91% with lenalidomide alone.

Currently, there is wide variation in approach to SMM, as well as debate regarding the impact of the 2 large randomized trials in terms of clinical practice. The 2 approaches, prevention versus curative intent, are both reasonable and are being investigated in the context of clinical trials, but only the prevention approach currently has randomized phase II data supporting its use. Based on this level of evidence, it is critically important that patients undergo modern imaging in addition to simple risk stratification to provide to them the risk of progression based on their current data. For patients who fit into the highest risk category, enrollment in clinical trials is critical to help answer these questions, but in the absence of a clinical trial, it is now reasonable to consider limited duration therapy with lenalidomide with or without dexamethasone based on data from 2 large randomized trials.

Sagar Lonial, MD, is professor and chair, Department of Hematology and Medical Oncology, Emory University School of Medicine, and chief medical officer, Winship Cancer Institute of Emory University in Atlanta, Georgia. He served as a co-chair of the 24th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma hosted by Physicians’ Education Resource®, LLC (PER®).

REFERENCES

Clinical Implications
How to approach smoldering multiple myeloma
The current standard of care (SOC) for patients with asymptomatic smoldering multiple myeloma (SMM) is enrollment on a clinical trial or observation for 6 months.

Two randomized trials may impact the SOC:
- **Preventive:** E3A06 trial (NCT01169337)1
  - In patients with intermediate- to high-risk SMM, treatment with single-agent lenalidomide (Revlimid) versus observation, led to a 72% reduction in the risk of disease progression at 3 years.
- **Curative:** GEM-CESAR (NCT02415413)2
  - In patients with high-risk SMM (n = 90) 56% of those who completed induction and high-dose therapy followed by autologous stem cell transplantation achieved sustained minimal residual disease negativity. At median follow-up of 17 months, 94% of patients remain alive and progression free.

Action in practice:
- Modern imaging
- Risk stratification
- Patients who fit the highest-risk category should be enrolled in clinical trials for preventive or curative therapy

Novel Approaches Gain Ground in Diffuse Large B-Cell Lymphoma

by KRISTI ROSA

DESPITE ADVANCES MADE in the treatment of patients with diffuse large B-cell lymphoma (DLBCL), investigators are on a quest to move more novel agents through clinical practice. The emergence of CD19-targeted CAR T-cell therapies into the treatment paradigm, however, has led to high response rates and generated excitement within the space.

CAR T-CELL THERAPY OFFERS HOPE IN R/R DISEASE
CAR T-cell therapy is a “designer-treatment,” and its use will largely be restricted to transplant centers, said Moskowitz, physician-in-chief, Oncology Service Line, Sylvester Comprehensive Cancer Center, and professor of medicine, University of Miami Health System Miller School of Medicine in Florida. “Each center is convinced that their CAR T-cell therapy is the best.”

Currently, 2 CAR T-cell products are approved for use as third-line treatment in patients with R/R DLBCL: axicabtagene ciloleucel (axi-cel; Yescarta) and tisagenlecleucel (Kymriah).

These patients are eligible for clinical trials but they do not tend to perform well. The product has been found to induce a median overall survival (OS) of 25.8 months for patients with refractory large B-cell lymphoma, according to data from a 3-year analysis of the pivotal phase II ZUMA-1 trial (NCT02348216).2 At a median follow-up of 39.1 months, axi-cel boasted a 3-year OS rate of 47%, with approximately 60% of patients having relapsed or progressed. Prior findings from a 2-year analysis of the trial showed that treatment with the agent led to an ORR of 83% and a complete remission rate of 58%. At 2 years, the OS rate was 51% with axi-cel and the progression-free survival (PFS) rate was 39%.

Axi-cel received approval from the FDA in October 2017 for use in adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after ≥2 prior lines of therapy. The product has been found to induce a median overall survival (OS) of 25.8 months for patients with refractory large B-cell lymphoma, according to data from a 3-year analysis of the pivotal phase II ZUMA-1 trial (NCT02348216).2
for use in adult patients with R/R large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL). The regulatory decision was based on data from the pivotal phase II JULIET trial (NCT02445248), which showed that treatment with the product led to an ORR of 50% (95% CI, 38%-62%) in those with R/R DLBCL.\(^3\) Updated data from the trial, which were published in the *New England Journal of Medicine*, showed a best ORR of 52%, with 40% of patients achieving complete response (CR) and 12% achieving partial response (PR).\(^4\) The estimated rate of PFS at 12 months with the product was 83% among those who had experienced a CR or PR at 3 months. Moreover, the estimated probability of survival at 12 months was 40%.

The ongoing phase III ZUMA-7 trial (NCT03391466) is evaluating whether treatment with axi-cel will improve the clinical outcomes for patients with R/R DLBCL compared with standard-of-care second-line therapy, which is comprised of platinum-containing salvage chemotherapy followed by high-dose therapy and ASCT in responders.

Despite the promise seen with CAR T-cell products, more work is needed to improve outcomes with this approach, according to Moskowitz. For one, smarter, more controllable CAR T cells must be developed. Further, pairing these products with additional agents, such as checkpoint inhibitors or Bruton tyrosine kinase inhibitors, might boost responses in patients. More research should also be dedicated to the development of universal CAR T cells, potentially available off-the-shelf products, which would allow

**TABLE. Novel Antibody Therapies for DLBCL\(^6,8\)**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Patient Population; Therapy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu5F9-G4 (5F9)</td>
<td>CD47</td>
<td>R/R B-cell NHL (DLBCL, n = 15); rixtuximab + 5F9</td>
<td>ORR: 40% CR: 33% PR: 7% Median DOR: NR</td>
</tr>
<tr>
<td>Tafasitamab (MOR208)</td>
<td>CD19</td>
<td>DLBCL (n = 80); tafasitamab + lenalidomide, followed by tafasitamab</td>
<td>ORR: 60%* CR: 43% Median PFS: 12.1 months Median DOR: 21.7 months</td>
</tr>
<tr>
<td>Mosunetuzumab</td>
<td>CD20/CD3</td>
<td>R/R DLBCL/transformed FL (n = 47); mosunetuzumab monotherapy</td>
<td>ORR: 34% CR: 19.1% Duration of CR: NR</td>
</tr>
</tbody>
</table>

CR indicates complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; NR, not reached; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory.

*Per investigator.
Newly Approved And Investigational Agents Are Joining Ruxolitinib (Jakafi) for the Treatment of Patients With Myelofibrosis (MF) and May Provide Options for Patients Who Progress or Become Intolerant to Frontline JAK Inhibitors.

At the 24th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma, hosted by Physicians’ Education Resource®, LLC (PER®), Ruben Mesa, MD, director of the The University of Texas Health Science Center at San Antonio and MD Anderson Cancer Center, presented available and emerging therapy options for patients who require additional MF therapy following ruxolitinib.1

The JAK inhibitor landscape includes 2 agents that are approved for use in patients with MF in the first-line setting, with fedratinib (Inrebic) receiving the designation in 2019 for patients with intermediate-2 or high-risk primary or secondary MF.2

Other agents that may become available include pacritinib, which is being evaluated in the phase II/III PACIFICa trial (NCT03165734) for patients with primary or secondary MF, and momelotinib, under evaluation in the phase III MOMENTUM trial (NCT04173490) for patients with MF who were previously treated with a JAK-inhibitor.

Another antibody generating excitement in this space is tafasitamab (MOR208), an Fc-enhanced, humanized, anti-CD19 monoclonal antibody that has shown single-agent activity in patients with R/R DLBCL.

In the single-arm phase II L-MIND trial (NCT02399085), tafasitamab is being explored in combination with lenalidomide (Revlimid) in patients with R/R DLBCL.

Results from the primary analysis of the trial showed that treatment with the combination led to an ORR of 60%, with a CR rate of 43% in this patient population.7 Median PFS with the combination was 12.1 months with a median follow-up of 17.3 months, suggesting that many of the patients are experiencing durable treatment effects. The median DOR reported with the treatment was 21.7 months.

Lastly, mosunetuzumab is a CD20/CD3 bispecific antibody that is designed to direct T cells to engage and kill malignant B cells. In a phase I/IIb trial, the antibody was shown to induce promising response rates in patients with DLBCL and FL.4 In those with DLBCL or transformed FL, the ORR was 34.0% with the agent, whereas the CR rate was 19.1%; the ORR and CR rates were 69.2% and 38.5%, respectively, in those with R/B FL.

“The why am I still passionate about the Hodgkin lymphoma and DLBCL research programs?” Moskowitz asked during his presentation. “They’re our chance to mentor the future leaders in lymphoma.”

For a full list of references, see the article at OncLive.com/link/7458.

Expanded Choices Emerge for Myelofibrosis Following Ruxolitinib Therapy

by AUDREY STERNBERG
CONTINUED CARE WITH RUXOLITINIB

A retrospective chart review of patients with MF who had received ruxolitinib at a single institution indicated that clinical characteristics of patients at the end of therapy showed significantly lower platelet counts, lower hemoglobin levels, and smaller spleen size. In addition, patients were more likely to be transfusion dependent and were more prone to abnormal cytogenetics such as a complex karyotype. However, platelet counts were the only clinical variable that could be tied to survival rates after discontinuation.³

Rechallenging patients with ruxolitinib therapy may be a viable treatment option for some who initially lose or have an inadequate response to the JAK1/2 inhibitor. In a cohort of 13 patients, the first rechallenge led to 9 (69%) experiencing spleen size reduction and all but 1 (92%) having improvement in constitutional symptoms. Four patients went on to receive a second rechallenge with ruxolitinib. According to Mesa, this analysis potentiates the idea of using a treatment “holiday” to reinduce responses in these patients.⁴

SINGLE AGENTS AFTER RUXOLITINIB

Data reported at the 2019 American Society of Hematology (2019 ASH) Annual Meeting revealed patient subsets for whom fedratinib may be the most suitable option in treating MF.

An analysis of patients treated with fedratinib in the frontline setting in the pivotal phase III JAKARTA trial (NCT01437787) and those treated post-ruxolitinib in the phase II JAKARTA2 trial (NCT01523171) demonstrated that platelet counts at baseline did not significantly affect treatment, and all treated patients achieved similar spleen volume and symptom response rates. These results indicate that fedratinib may offer promise to patients with low platelet counts who would otherwise have disappointing responses.⁵

Upon a reanalysis of JAKARTA2, baseline disease-characteristic data indicate that fedratinib was associated with clinically meaningful and statistically significant reductions in splenomegaly and symptom burden in patients with MF who met stringent criteria for being ruxolitinib refractory or intolerant.⁶

The investigational agent IMG-7289—an inhibitor of the lysine-specific histone demethylase 1A (LSD1), which is an epigenetic regulator critical for self-renewal of malignant myeloid cells and differentiation of myeloid progenitors—was examined in a phase I/II trial of patients with high- or intermediate-2 risk MF that is resistant or intolerant to available therapies. In 9 evaluable patients, 66% had spleen reduction and 56% had ≥50% total symptoms scores (TSS).⁷

Combination therapy treatment strategies that combine ruxolitinib with other agents have also shown promise in the setting of intolerance or relapse. At 2019 ASH, data revealed that the small molecule BET inhibitor CPI-0610 demonstrated a favorable safety profile and clinical benefit when combined with ruxolitinib in the treatment of patients who had inadequate or no response to or who were refractory to ruxolitinib. Additionally, bone marrow fibrosis improvement and anemia response indicate that this strategy has the potential to result in meaningful disease modification in certain patients. In patients who were transfusion dependent (TD) and relapsed/refractory or intolerant to ruxolitinib, 25% had spleen reduction of ≥35% (SVR35) with a median change of -24.9%. Six out of 14 patients converted from TD to transfusion independent (TI).⁸

Additional data presented at the meeting showed that the small molecule inhibitor navitoclax added to ruxolitinib induced clinically meaningful spleen responses and symptom improvement in patients with primary or secondary MF and resistance to ruxolitinib in the frontline setting. At 24 weeks, SVR35 was achieved by 30% of patients, with an additional 53% having resolution of palpable splenomegaly. Additionally, navitoclax was successful in reducing the TSS in most patients at 24 weeks compared with the baseline (7 TSS vs 12 TSS).⁹

CONCOMITANT THERAPY FOR ANEMIA

Due to high rates of anemia requiring red blood cell transfusions in both primary and secondary MF, therapeutic strategies to get patients to be TI are needed.

The results of a phase II trial of luspatercept-aamt (Reblozyl) in patients with MF and anemia were reported at 2019 ASH, with clinically significant activity of luspatercept seen in patients regardless of ruxolitinib therapy. The primary end point in patients not receiving transfusions was a hemoglobin increase of 1.5 g/L or more at every assessment from baseline for 12 or more consecutive weeks within the first 24 weeks. In patients receiving transfusions, the primary end point was TI for 12 or more consecutive weeks within the first 24 weeks. Patients who received ruxolitinib and did not require transfusions achieved the primary end point at a rate of 21% versus 32% of patients who did. Those not receiving ruxolitinib achieved the primary end point at rates of 14% and 10%, respectively.¹⁰

Mesa concluded by reviewing clinical scenarios in which each agent might find its niche. Based on National Comprehensive Cancer Network guidelines, fedratinib is the only officially recommended therapy following ruxolitinib failure.¹¹ However, based on promising data, other JAK inhibitors, combination therapy with ruxolitinib, concomitant therapy, and investigational single agents could join the paradigm.
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Investigators Seek to Improve SOC in Cervical Cancer

By RACHEL NAROZNIAK, MA

MOTIVATED TO MOVE THE needle in cervical cancer, investigators are adding durvalumab (Imfinzi) to standard-of-care concurrent chemoradiation therapy (SOC CCRT) and brachytherapy to determine whether PD-L1 blockade is a key to improving survival outcomes.

“The National Cancer Institute issued a consensus statement more than 20 years ago changing the standard of care [SOC] for locally advanced cervical cancer from radiation alone to concurrent chemoradiation, and we still remain in the same treatment paradigm,” said Jyoti S. Mayadev, MD, a radiation oncologist at the University of California (UC) San Diego Health.

The phase III CALLA study (NCT03830866) is currently active and expects to enroll approximately 714 immunotherapy-, chemotherapy-, and radiotherapy-naïve patients with histologically confirmed cervical adenocarcinoma or squamous carcinoma. Patients will be randomized to receive CCRT with or without durvalumab followed by brachytherapy.

As one of the largest clinical trials in this patient population with more than 130 sites outside the United States, CALLA “has the potential to have a grand impact on the burden of cervical cancer” because it affords investigators the ability to deliver novel therapeutic treatments to patients throughout the world, said Mayadev, the principal investigator of CALLA’s site at UC San Diego Health.

Better screening techniques and increased immunization against the human papillomavirus (HPV), which is thought to be the primary driver of the disease, has caused cervical cancer rates to decrease among women in the United States. However, incidence continues to be high in developing countries where 85% of cases are diagnosed because screening is not as widely available as it is in the United States.

In 2019, it was estimated that there would be about 13,170 new cases of cervical cancer in the United States and 4250 deaths from the disease. Nationwide, the 5-year relative survival rate for patients with distant disease is 16.9% versus 91.8% for localized disease.

THE CURRENT PARADIGM

Treatment that includes surgery and CCRT, can lead to cures in 80% of women with stage I to stage II disease (early stage) and in 60% of women with stage III disease. Patients with early-stage disease, defined as cancer that is less than 4 cm in size, typically undergo surgery.

“Depending on the risk factors at the time of surgery, we may give radiation or a combination of radiation and chemotherapy after surgery,” Mayadev said.

Patients with stage Ib2 or higher disease generally receive CCRT.

“Because the disease has usually gone outside of the cervix, patients are no longer candidates for surgery and are instead treated with a combination of cisplatin-containing chemotherapy once weekly at 40 mg/m² and daily radiation,” Mayadev explained.

CCRT is followed by brachytherapy, a type of internal radiation therapy that delivers radiation in and around the tumor and delivers a high dose of radiation after the external beam radiation therapy (EBRT) that patients receive during CCRT. Brachytherapy is used to intensify the anticancer effect of prior EBRT in this nonoperable patient population.

“The increase in dose that you get from brachytherapy cannot be mimicked with external radiation and patients with cervical cancer who receive brachytherapy have shown an improvement in survival versus those who did not get brachytherapy,” Mayadev said.

Findings from a retrospective study of 7359 patients with stage Ib2 to stage Iva cervical cancer confirmed the survival benefit conferred by EBRT and subsequent brachytherapy. Brachytherapy was associated with better overall survival (OS) than radiation treatment consisting only of EBRT (58.2% vs 46.2%; P < .001). Most patients (63%) received EBRT followed by brachytherapy. The remaining 37% concluded their radiation therapy with EBRT.

Despite the documented efficacy of EBRT and later brachytherapy, brachytherapy’s

FIGURE. Durvalumab and Chemoradiotherapy in Locally Advanced Cervical Cancer

PHASE III CALLA TRIAL (NCT03830866)

Control Arm: SOC CCRT

N = 714

- PFS
- OS
- CR rate
- ORR
- DOR in patients with a CR
- HRQOL
- PFS at 3 years

Experimental Arm: Durvalumab + SOC CCRT followed by durvalumab monotherapy

Eligibility Criteria

- ≥18 years, female
- Cervical adenocarcinoma or squamous carcinoma FIGO (2009) stage Ib2-Iib node-positive or IIa-Iva of any node
- ≥1 lesion that qualifies as a RECIST (version 1.1) target lesion at baseline and has not been previously irradiated
- No prior chemotherapy or radiotherapy for cervical cancer
- WHO/ECOG PS of 0-1

CCRT indicates concurrent chemoradiation therapy; CR, complete response; DOR, duration of response; FIGO, International Federation of Gynecology and Obstetrics; HRQOL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; SOC, standard of care; WHO, World Health Organization.
uptake is still low in cervical cancer, Mayadev said. “We’ve done a lot of research on the number of patients who get brachytherapy and found it to be around 50% in California, so we have to make a lot of strides within cervical cancer,” she added. “We need to make sure that all patients are offered brachytherapy.”

CALLA investigators will give EBRT-include CCRT in both arms of the CALLA study. Patients randomized to the experimental arm will receive intravenous durvalumab at 1500 mg every 4 weeks for 96 weeks followed by durvalumab monotherapy for up to 24 months or until progression from the date of randomization.¹

All patients will receive either pelvis- or pelvis and para-aortic-directed CCRT at 45 Gy. Afterward, brachytherapy will be initiated in tandem with 40 mg/m² of cisplatin or carboplatin-based chemotherapy once weekly for 5 weeks. Patients will have the option to receive a sixth dose of therapy.³

Randomization will be stratified by disease stage and geographic region.¹ The primary end point is progression-free survival. OS and the objective and complete response rates are among the CALLA study’s several secondary end points (FIGURE).

To be eligible to enroll in the CALLA trial, patients must have locally advanced disease that meets the 2018 International Federation of Gynecology and Obstetrics criteria for stage Ib2 to IIN node-positive disease or stage IIIa to stage IVa disease with any node.

Although CCRT is “very curative” for node-negative early-stage disease, said Mayadev, the SOC for patients with later-stage node-positive cervical cancer is not sufficient.

“The need for a new treatment option is great. Patients with stage IIIa to stage IVa node-positive cervical cancer, particularly those with periaortic lymph node metastasis represent a particularly poor prognostic group,” Mayadev said. This subset has high rates of systemic relapse and poor survival: the 3-year OS rate ranges from 30% to 50%, according to Mayadev.

For patients with periaortic lymph node metastasis, the survival rate is approximately 50% after CCRT and brachytherapy, Mayadev added. “We really want to push the needle for these patients who present with nodal-positive disease,” she said.

**BOOSTING IMMUNOGENICITY**

The hope of meeting the existing global need in cervical cancer and the antitumor activity that the addition of durvalumab to the SOC could promote propelled the development of the CALLA trial, Mayadev said.

Investigators hypothesize that, when combined with CCRT, PD-L1/PD-L1 pathway blockade may augment immunogenicity by increasing phagocytosis, antigen presentation, and ultimately, cell death.³ Cancer cells evade the immune system by disrupting phagocytosis, a process of foreign substance eradication and dead cell clearance enacted by a type of white blood cell known as a phagocyte. Phagocytosis is necessary for the detection and removal of malignant cells.³ eight.

Antigen presentation is also critical to tumor-targeting approaches in cancer treatment. Downregulation or loss of antigen presentation enables tumor cells to avoid immune recognition, preventing antitumor T cells from seeking and destroying these cells.³

Most cervical cancers have a viral etiology, which compromises immune system function.⁴ Durvalumab could offset this immunogenic compromise and “reactivate immune-mediated tumor surveillance, translating to increased antitumor activity,” Mayadev explained.

Durvalumab is a PD-L1 inhibitor. PD-L1 interaction with PD-1 and CD80 prevents T-cell function and activation. Blockade of these PD-L1/PD-1 and PD-L1/CD80 interactions releases inhibited immune responses, supporting immune system activity. This mechanism of action makes durvalumab an attractive option to further investigate in the treatment of cervical cancer.¹⁰,¹¹

The drug currently is approved in locally advanced or metastatic urothelial carcinoma and in unresectable stage III non-small cell lung cancer settings.

The rationale for using immunotherapy in cervical cancer is also based on the nature of the disease. “Cervical cancer is highly immunogenic, and we know that virtually all cases of cervical cancer are induced by chronic HPV infection that develops with the activation of adaptive immune systems,” Mayadev said.

HPV is the most common sexually transmitted disease in the United States and manifests in both a low- and high-risk form. Of note, only high-risk HPV causes cancer. To date, 13 HPV types have been identified as cervical cancer drivers. Usually, the immune system naturally rids itself of the HPV infection within a 2-year period. However, when it cannot, the extended presence of the infection can convert healthy cells into abnormal cells, which eventually become cancerous.¹²

Although preventive immunizations such as the HPV 9-valent vaccine (Gardasil 9) can help protect individuals from cancer-associated strains of HPV, CALLA investigators hope that the addition of durvalumab to the SOC will offer promise to those with cervical cancer.

“We’re hoping that immunotherapy will be the next potential breakthrough in cervical cancer,” Mayadev said.

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

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**Hayes on Immunotherapy Research in Gynecologic Cancers**

The role of immunotherapy in the treatment of gynecologic cancers is evolving, according to John Hayes, MD, PhD. Ongoing trials investigating immunotherapies in combination with targeted therapies may soon provide results for this patient population, said Hayes, an assistant professor and member of the Translational Therapeutics Program at The Ohio State University.

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Clinical Perspectives | GI Cancers

Novel Combinations Make Their Mark in HCC

by Jason Harris

Novel Combinations of therapies for hepatocellular carcinoma (HCC) have shown positive impact on survival, but they can also increase adverse events (AEs), said Ghassan K. Abou-Alfa, MD.

Abou-Alfa, a medical oncologist at Memorial Sloan Kettering Cancer Center, discussed recent studies of combination therapies for HCC at the 2020 HCC-TAG Conference. For example, the phase III IMbrave 150 trial (NCT03434379) showed that the combination of atezolizumab (Tecentriq) plus bevacizumab (Avastin) improved overall survival (OS) versus sorafenib (Nexavar) in patients with unresectable HCC. These findings represented the first time a treatment outperformed sorafenib for OS and progression-free survival (PFS) in this setting, and the HCC world was understandably excited, he said.1

Abou-Alfa said the combination will likely overtake sorafenib as the standard of care in the first-line setting at some point. However, he cautioned about making too much of the data pending further validation.

“This is positive data, but I’m always cautious...waiting to see the full data,” he said. “What we are depending on so far is an abstract. We need more data to see the analysis in depth to put it in place and compare it with other agents.”

Abou-Alfa took his audience on a recap of the triumphs and challenges of 2019 in HCC—with IMbrave 150 being the most significant development—and set the stage for the year ahead.

Doublet versus Monotherapy

In IMbrave 150, 501 patients with unresectable HCC were randomly assigned to 1200 mg of intravenous (IV) atezolizumab plus 15 mg/kg of IV bevacizumab every 3 weeks or 400 mg of sorafenib by mouth twice daily. Patients stayed on the study until unacceptable toxicity or loss of clinical benefit.

At a median follow-up of 8.6 months, investigators observed a 42% decrease in the risk of death (HR, 0.58; 95% CI, 0.42-0.79; \( P = .0006 \)) and a 41% decrease in the risk of disease progression or death (HR, 0.59; 95% CI, 0.47-0.76; \( P < .0001 \)) in the atezolizumab/bevacizumab arm versus the sorafenib arm.2 At the median PFS of 6.8 months in the experimental arm and 4.3 months in the control arm. The median OS was not reached versus 13.2 months, respectively.

Compared with the sorafenib arm, the overall response rate (ORR) was greater in the combination arm (27% vs 12%; \( P < .0001 \)) based on independent assessment using RECIST 1.1 criteria and similarly increased using HCC mRECIST criteria (33% vs 13%; \( P < .0001 \)).

Subsequent findings presented at the 2020 Gastrointestinal Cancers Symposium in January showed that atezolizumab/bevacizumab confers benefits in quality of life, functioning, and key symptoms compared with sorafenib.3

Doublet versus Triplet

While sorafenib and lenvatinib (Lenvima) remain the only approved agents for HCC in the upfront setting, Abou-Alfa said combinations—anti-VEGF agents plus checkpoint inhibitors, tyrosine kinase inhibitors plus checkpoint inhibitors, and dual checkpoint inhibitors—are “novel, positive, and disruptive.” He pointed to data from the phase I/II CheckMate-040 trial (NCT01658878) to show the potential impact of the doublet of nivolumab (Opdivo) plus cabozantinib (Cabometyx), and the triplet regimen combining nivolumab with ipilimumab (Yervoy) and cabozantinib.

Previous data from another cohort from the trial showed that nivolumab in combination with ipilimumab demonstrated a high response rate and durable responses in patients with advanced HCC previously treated with sorafenib.4 Moreover, a previous pivotal phase III study of cabozantinib in patients with advanced HCC showed a median OS of 10.2 months.5

In findings from CheckMate-040 presented at the 2020 Gastrointestinal Cancers Symposium, the median PFS by investigator assessment was 6.8 months (95% CI, 4.0-14.3) with nivolumab/ipilimumab/cabozantinib (n = 35) versus 5.4 months (95% CI, 3.2-10.9) with nivolumab/cabozantinib (n = 36). The median OS was 21.5 months (95% CI, 13.1 to not reached) with the doublet and not reached with the triplet (95% CI, 15.1 to not reached). The 15-month OS rates also favored the triplet (70% vs 64%).6

However, the triplet was associated with a higher rate of treatment-emergent AEs. Twenty-five (71%) patients in the triplet arm experienced grade 3/4 treatment-related AEs compared with 17 (47%) in the doublet arm. The rate of discontinuation due to toxicity was nearly twice as high in the triplet arm (20% vs 11%), as was discontinuation for immune-related AEs (11% vs 6%).

“The one thing that caught our attention quite a bit was the adverse events—quite a high level of grade 3/4 toxicity with the triplet,” Abou-Alfa said. He added that the toxicity profile means that the triplet will require further study before its therapeutic role can be defined.

For a full list of references, see the article at OncLive.com/link/7628.
Hope is in bloom in RET+ NSCLC

Test for RET and other biomarkers to impact treatment plans.1,2

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Targeted therapies for biomarkers like EGFR and ALK are available.3,4 Other biomarkers, like RET, represent a growing list that we’re learning more about in non–small cell lung cancer (NSCLC).5 Molecular profiling, including next-generation sequencing (NGS), can reveal which biomarkers could be driving disease.5

Treating based on targeting specific biomarkers may lead to improved patient outcomes for your NSCLC patients.2,6

Tumor Type May Predict Response in Metastatic Hormone-Sensitive Prostate Cancer

**by DANIELLE TERNYILA**

**TREATMENT OUTCOMES FOR** patients with metastatic hormone-sensitive prostate cancer (mHSPC) who receive androgen-deprivation therapy (ADT) alone or in combination with docetaxel differ depending on the tumor subtype, according to study findings. Patients with mHSPC with a luminal B tumor have better outcomes with the addition of docetaxel to ADT compared with ADT alone than do those with basal tumors, investigators reported at the 2020 Genitourinary Cancers Symposium. The results also showed that the basal tumor subtype predicts a lack of survival benefit from docetaxel therapy.1

In this analysis, gene expression profiling was conducted on biopsy samples from patients who participated in the phase III E3805 CHAARTED clinical trial (NCT00309985), in which patients with mHSPC received either ADT alone or in combination with docetaxel. The correlative study was conducted to determine potential biomarkers of response in this patient population. Of 160 patients who underwent profiling, 77 had luminal B tumors (48%), 80 had basal tumors (50%), and 3 patients had luminal A tumors (2%). Patients in the luminal B and basal subtype groups had similar high volumes of disease.

In the ADT-only arm, patients with the luminal B subtype had a shorter median OS of 29.8 months compared with 47.1 months for those who had the basal subtype (HR, 1.75; 95% CI, 0.99-3.10; P = .052). In the ADT plus docetaxel arm, patients with the luminal B subtype achieved a median OS of 52.1 months versus 49.2 months for those with the basal subtype (HR, 0.92; 95% CI, 0.49-172; P = .14).

In an interview with OncologyLive®, Anis Hamid, MBBS, medical oncologist and genitourinary oncology research fellow at Dana-Farber Cancer Institute in Boston, Massachusetts, discussed the implications of these findings.

**What were the key findings from the CHAARTED study?**

**What do these data tell us about the luminal B subtype?**

We know a little about luminal and basal subtypes from initial work done in localized nonmetastatic prostate cancer where luminal A, luminal B, and basal subtypes comprised approximately a third each in that population. In the CHAARTED population in the mHSPC [group] population, we saw that there were few luminal A tumors and most of the tumors were either luminal B or basal.

Luminal B tumors were associated with a shorter survival on hormonal therapy alone. However, that subtype specifically benefited from up-front docetaxel chemotherapy. On the other hand, basal tumors were associated with a relatively better prognosis compared with luminal B tumors, but when we looked at outcomes with chemotherapy, we didn’t observe a significantly beneficial response to up-front chemotherapy. In this way, it looks like luminal B and basal subtyping not only have prognostic effects but also a predictive potential.

**How was CHAARTED conducted?**

The CHAARTED trial was a phase III randomized trial of men with newly diagnosed mHSPC. This trial was reported about 6 years ago, and before that time, the standard of care for men with metastatic disease was androgen-deprivation therapy or hormonal therapy. The CHAARTED trial showed that the addition of docetaxel therapy given at the start of diagnosis significantly improved the survival of men with newly diagnosed metastatic prostate cancer.

Since CHAARTED and related trials, such as STAMPEDE and others, docetaxel became the standard treatment for men with metastatic prostate cancer. Several treatments have been introduced in a similar setting, including potent hormonal therapies, such as abiraterone acetate [Zytiga], enzalutamide [Xtandi], and apalutamide [Erleada].

**What other therapies may show a benefit for the luminal B subtype?**

We know that the luminal B subtype appears to benefit from docetaxel. One of the important questions is whether these luminal B and basal subtypes respond similarly with potent hormonal therapies that we have in clinic, such as abiraterone, enzalutamide, or apalutamide. Luckily, we are partnered with trials that have tested these drugs in a prospective setting, and hopefully, we will learn once we have more information from the RNA profiling of those studies.

**What other questions do you hope to answer in the near future?**

There are layers of biological information about genomics, such as epigenomics and, for example, how demethylation might affect treatment response and prognosis. We are hoping to integrate multiple layers of biological information across independent cohorts to get a more multidimensional view of the biomarkers that might guide precision care for these patients.  

**REFERENCE**

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Navigating the Personalized Medicine Landscape in Advanced NSCLC

by ELLIE LEICK

SIGNIFICANT RESEARCH ADVANCES

in targeted therapy and immunotherapy in the past few years have created more molecularly selected treatment for patients with advanced non–small cell lung cancer (NSCLC). However, personalized approaches require waiting for genetic results, and some patients cannot afford to delay treatment, according to Heather A. Wakelee, MD.

The National Comprehensive Cancer Network guidelines for NSCLC recommend broad molecular profiling to evaluate for actionable mutations in patients with NSCLC. First-line treatment options are available for patients harboring EGFR, ALK, or ROS1 aberrations.

Though comprehensive molecular testing provides critical information for treatment decisions, results take 1 to 3 weeks to arrive. For patients who require immediate treatment, there are little data to support a concrete next step. In these scenarios, Wakelee said, she recommends chemotherapy, which, although not the optimal option, will not cause harm.

In an interview with OncologyLive® during the 2020 Winter Lung Conference®, hosted by Physician’s Education Resource®, LLC (PER®), Wakelee, a professor of medicine at Stanford Health Care in Palo Alto, California, discussed treatment advances in advanced NSCLC and recommendations for specific clinical scenarios.

For patients who require immediate treatment but are awaiting molecular testing results, what do you recommend?

With new diagnoses, there are 2 factors that you have to take into account: physical and psychological factors of the patients. Some patients, by the time they present, are quite ill. They have a high tumor burden and might have painful bone metastases or liver metastases or have difficulty breathing. In this case, you cannot wait 2 more weeks [to administer therapy] because they won’t be well enough to even get treatment.

Then you are forced to start to pick a treatment. That’s where you have to be a little bit less evidence based. If there is a high suspicion that they have a driver mutation, I’m going to treat that patient with chemothermy, maybe with bevacizumab [Avastin], but not with immunotherapy. I don’t want to give them immunotherapy and then find out 3 weeks later that they actually have an ALK translocation. I’m going to be limited in which ALK-targeted drug I can use because of the reaction to the immunotherapy that’s already in their system. The same applies to EGFR. In that setting, I’ll wait.

With someone who is very unlikely to have a driver mutation, then I might think about giving chemotherapy plus immunotherapy because I cannot wait to start. Occasionally, you can’t even do that because sometimes the payers are going to say, “I’m not giving chemotherapy plus immunotherapy because I know there’s no driver.” Then you’re a little bit stuck. You can always give chemotherapy. Chemotherapy is never a wrong choice. It may not be the best choice, but if you don’t know, then it’s an OK choice. For patients who physically need to get started on therapy, that’s how I think about it.

For patients who psychologically need to get started, which is a much bigger group, I spend time talking with them about the fact that I could start doing chemotherapy today, which is an OK choice. However, if I understand the whole tumor by getting those driver mutations, I can perhaps pick a better therapy or at least not be worried that I’m picking one that’s not as good. Most people are OK with that, but you need to see them at least once a week in clinic and keep coaching them and check in on them.

Most of the tissue testing can still take 2 to 3 weeks to come back. People are working on making it faster, but it’s still slow. Many of the liquid biopsies looking at circulating tumor DNA have results that come back faster, but they are not always being covered by the payers. It’s going to depend on whether the patient is willing to take a gamble of potentially spending several thousand dollars. It’s complicated because sometimes those costs will be covered in different ways.

In general, those are the conversations that we have to have. I would like to get to a point where we can do the tissue testing and plasma testing simultaneously, knowing that some of the time we will get redundant information. However, sometimes we will get a much better story about the whole issue with the tumor and how much it is shedding, or whether we happened to biopsy 1 portion that didn’t have the whole story about the mutations. That’s my ideal world, but I don’t always get to do that for my patients.

What are some recent advances in targeted therapy?

Many advances have happened in a targeted revolution. [Targeted therapy has been around] almost been 20 years now. I don’t think most people can imagine treating a patient with advanced lung cancer without knowing their driver mutations. For a while, we have known to look for EGFR [mutations] and treat these patients with EGFR TKIs [tyrosine kinase inhibitors] instead of chemotherapy. More recently, the FLAURA data showed us that osimertinib [Tagrisso] is perhaps a better EGFR TKI to start with because of the longer duration of response and the improved overall survival compared with some of the other EGFR TKIs [NCT02296125]. In general, for the patients, osimertinib is better tolerated, although we do need to be mindful about cardiac and other toxicities.

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HER2+ Breast Cancer Treatment Arsenal Expands With ADCs

by ELLIE LEICK

THERAPEUTIC OPTIONS FOR patients with HER2-positive breast cancer have expanded over the last decade, leading to improved outcomes across patient subgroups and transitioning the malignancy to a more long-term disease, experts say.

“HER2-positive breast cancer comprises about 15% to 20% of all metastatic breast cancers, but HER2-positive breast cancer isn’t 1 disease. We’re beginning to see that there are subtypes even within that subtype,” explained Sara A. Hurvitz, MD, an associate professor at the David Geffen School of Medicine and medical director of the Jonsson Comprehensive Cancer Center Clinical Research Unit at the University of California, Los Angeles (UCLA).

Antibody-drug conjugates (ADCs) have been garnering interest in HER2-positive disease for some time. Ado-trastuzumab emtansine (T-DM1; Kadcyla), for example, is approved as an adjuvant treatment for patients with HER2-positive early breast cancer who have residual invasive disease following neoadjuvant trastuzumab (Herceptin) and chemotherapy. It is also indicated for patients with metastatic disease who previously received treatment with trastuzumab and a taxane.

Most recently, fam-trastuzumab deruxtecan-nxki (Enhertu) received an accelerated approval from the FDA in December 2019 for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received ≥2 prior anti-HER2-based regimens in the metastatic setting (TABLE).

The approval was based on findings from the phase II DESTINY-Breast01 trial, which showed that trastuzumab deruxtecan had an objective response rate (ORR) of 60.3% per independent central review in heavily pretreated patients with advanced HER2-positive breast cancer.

Additionally, the median duration of response was 14.8 months (95% CI, 13.8-16.9), and the disease control rate was 97.3% (95% CI, 93.8%-99.1%). At a median follow-up of 11.1 months, the median progression-free survival (PFS) was 16.4 months; in the 24 patients with brain metastases, the median PFS was 18.1 months. The median overall survival (OS) was not reached.

“The reason that [ADCs] work well is that if a tumor is driven by HER2, you’re guiding a missile to the HER2-positive breast cancer cell,” said Neelima Denduluri, MD, a medical oncologist at Virginia Cancer Specialists.

In interviews with OncologyLive®, Hurvitz, Denduluri, and Madelaine Kuiper, MSN, RN, an advanced nurse practitioner at Ronald Reagan UCLA Medical Center and Santa Monica UCLA Medical Center, discussed the rise of HER2-targeted therapies and their implications on the field.

How has HER2-positive breast cancer treatment evolved over the past few years?

Hurvitz: HER2-positive metastatic breast cancer has seen a revolution in the way that it’s treated, especially in the last decade. In the last several years, we have seen the introduction of novel agents that have moved the needle over to extending OS. The introduction of pertuzumab (Perjeta) when added to trastuzumab and a taxane from the CLEOPATRA study saw a median OS of [nearly] 5 years. When I was in training, we were excited if a patient survived 2 years. To see that the median OS had moved by several years was really impressive. Now, because we know the HER2 target is so important to go after in HER2-driven disease, there have been multiple agents that have been developed for this breast cancer, including selective HER2 TKIs [tyrosine kinase inhibitors] such as tucatinib, novel ADCs, such as T-DM1, and now trastuzumab deruxtecan.

Denduluri: In the past, we always knew that the HER2 oncogene conferred a poor prognosis for patients, but we didn’t have a good way to target it. About 20 years ago, trastuzumab started being incorporated into patient care. For the [past] 14 years, we’ve been using it routinely to reduce the risk of early breast cancer coming back. We also knew that those who had stage IV or metastatic breast cancer had a poor prognosis when they had HER2-positive disease. In the advent of HER2-positive targeted therapy, including trastuzumab and pertuzumab, HER2-positive breast cancer has truly become a [long-term] disease where the median survival is about 5 years and about 40% of patients are alive 8 or more years later—but by no means is a “home run.” At the same time, the progress has been dramatic. We have more targeted molecules.

Kuiper: [The paradigm has] changed rapidly. I remember in the 1980s when [these drugs were] new and we started actually treating patients. Even in the [past] 6 years that I’ve been working in breast cancer, there has been a rapid development of HER2-targeting therapies, including T-DM1, pertuzumab, neratinib [Nerlynx], and tucatinib. Now, we have trastuzumab deruxtecan. It’s amazing how many drugs are looking very positive in this setting and expanding treatment options for patients.

How are ADCs utilized in HER2-positive treatment?

Hurvitz: We previously had 1 approved ADC for breast cancer: T-DM1. T-DM1 causes the HER2 antibodies to stably link to a cytotoxic payload, which is a derivative of maytansine; this is a microtubule poison. T-DM1 was approved for [patients with] metastatic breast cancer in 2013. Results from the EMILIA study showed that T-DM1 improved PFS and OS compared with lapatinib (Tykerb)/capecitabine (Xeloda). [T-DM1] is now the gold standard for second-line therapy. First-line therapy is taxane, trastuzumab, and pertuzumab, and when a patient’s disease progresses, they move to T-DM1.

We have recent results relating to trastuzumab deruxtecan, which received accelerated approval in December 2019. There was a phase II, single-arm study called DESTINY-Breast01, which demonstrated an impressive ORR and median PFS in very heavily pretreated patients.
**TABLE.** Approved ADCs for HER2-Positive Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Antibody-Drug Conjugate</th>
<th>Mechanism of Action</th>
<th>Indication(s)</th>
<th>Black Box Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ado-trastuzumab emtansine (T-DM1; Kadcyla)</td>
<td>The antibody is the humanized anti-HER2 IgG1, trastuzumab. The small molecule cytotoxin, DM1, is a microtubule inhibitor.</td>
<td>• The treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination</td>
<td>• Hepatotoxicity, liver failure, and death have occurred in T-DM1 treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate.</td>
</tr>
<tr>
<td>[Fam-] trastuzumab deruxtecan-nkki (Enhertu)</td>
<td>The antibody is a humanized anti-HER2 IgG1. The small molecule, DXd, is a topoisoeraser I inhibitor attached to the antibody by a cleavable linker.</td>
<td>• The treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2–based regimens in the metastatic setting</td>
<td>• ILD and pneumonitis, including fatal cases, have been reported. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue use in all patients with grade 2 or higher ILD/pneumonitis. • Embryo-fetal toxicity</td>
</tr>
</tbody>
</table>

ADCs indicates antibody-drug conjugates; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction.

**Denduluri:** The most commonly used ADC [in HER2-positive breast cancer] is T-DM1. However, trastuzumab deruxtecan was recently approved after showing significant activity in a heavily pretreated population. There are also several [ADCs] that are being developed. One agent in the pipeline is called SYD985.

**Kuiper:** It’s a new and great opportunity to look at how we can utilize therapies and perhaps combine them. One of the first ADCs was T-DM1, with a true smart bomb effect, which gave an opportunity to use a drug that was not too toxic. Now, looking at trastuzumab deruxtecan, it’s a great opportunity for patients in further lines of therapy.

**Could you explain the mechanism of action of ADCs and what makes them so effective?**

**Hurvitz:** ADCs are a very exciting modality of treatment because they pair with a very specifically targeted antibody, which targets the tumor cells more specifically than normal cells. It combines a cytotoxic payload with that antibody, or links to that antibody, which is a very potent type of chemotherapy. This allows the chemotherapy to be directed to the antigen-overexpressing T cell. The thought is, if you can specifically direct the chemotherapy to the antigen-overexpressing T cell, you’re going to limit toxicity to the normal cells. We see that with drugs such as T-DM1, where patients are getting a very toxic type of chemotherapy, but because it is specifically targeting the HER2 antigen, patients don’t even have hair loss and generally feel quite well on it. They don’t have the typical adverse events (AEs) of a naked, cytotoxic chemotherapy.

**Could you review the DESTINY-Breast01 trial results with trastuzumab deruxtecan?**

**Hurvitz:** The DESTINY-Breast01 trial was a single-arm, phase II study evaluating patients with HER2-positive metastatic breast cancer, all of whom had received trastuzumab and T-DM1 in the metastatic setting. The patients had a median of 6 prior lines of therapy, making this an incredibly heavily pretreated patient population with metastatic breast cancer. In this study, they showed that using trastuzumab deruxtecan yielded an ORR of over 60%. This is unheard of. This is an ORR that we get excited about in a first-line metastatic study, so to see this in the third-line setting and beyond is very phenomenal. The median PFS was more than 16 months. Again, these are very impressive data in a setting where you expect patients to have a quick progression. However, ongoing phase III randomized trials will be important in defining where we should be utilizing this drug.

**Denduluri:** The DESTINY-Breast01 trial was a phase II trial in a heavily pretreated population where patients received trastuzumab and T-DM1; many patients had several lines of prior HER2-targeted therapy and chemotherapy. These patients were given trastuzumab deruxtecan and we saw that there was an ORR over 60%, which is unheard of in a population that is heavily pretreated.

It was extremely promising, and there was a group of patients that didn’t have to change therapy for about 10 months. The median PFS was over 16 months, which was extremely promising and very exciting. The toxicities associated with the drug are nausea; there was some alopecia. The most significant concern was interstitial lung disease (ILD). We know now that we must be on the lookout for it. We’re developing guidelines to manage ILD and manage the drug toxicity. We are looking forward to taking it to the next step of phase III studies and compare [this drug with] the current standard of care.

**Kuiper:** Trastuzumab deruxtecan seems to be very, very promising and exciting for patients. A lot of my patients are heavily pretreated and may not have so many options left now. This looks like a great option for...
these patients. I definitely think the DESTINY-Breast01 study shows very positive results, and it’s a drug that we will start to use more frequently now. I’m not sure where it will fit within the lines of therapy. I still have to talk to my physician about all of that. The safety profile is worrisome, but it is something that we’re all very aware of. We have to monitor and work with patients. I definitely think this is going to be good for us and good for patients.

Q: How can early detection of ILD be improved? How can it be best managed?

Hurvitiz: A number of different anticancer therapies are associated with ILD or pneumonitis. This is an AE that is potentially serious and life-threatening, so it needs to be recognized and managed early in order to prevent a severe outcome. Trastuzumab deruxtecan has been associated with pneumonitis, with some patient deaths in the early-phase clinical trials. Therefore, for patients who have a preexisting history of pneumonitis or ILD, we aren’t going to recommend this therapy for them.

When we evaluate patient scans while they are on therapy, if we begin to note ground glass opacities or other findings suggest pneumonitis, or if a patient develops a dry cough, fever, or shortness of breath, those [symptoms] would lead us to hold therapy while we evaluate. If a patient is shown to have more severe clinical symptomatic pneumonitis, we would use steroids and stop therapy. It is an important AE for us all to be aware of, not only with trastuzumab deruxtecan but also with immune-based therapies and other therapies that are being investigated in breast cancer.

Denduluri: Unfortunately, 4 patients died due to ILD and it is definitely a concern. The most important thing we can do to prevent and/or manage [this disease] is communicate with our patients—listen to them, and listen for respiratory issues, such as cough and shortness of breath. When we listen to them with our stethoscope, are we hearing anything? Physical exams are very important. What are we seeing on their scans? Once we recognize [ILD], then image it, hold the drug, implement steroids early, we then work in a multidisciplinary fashion with our pulmonologist. If it’s very severe, then the drug needs to be stopped.

Kuiper: I educate my patients. Those with ILD tend to present with a dry cough that’s persistent—it doesn’t get better with whatever you do for it—and shortness of breath. One of my discussions with the patient is if you develop these symptoms, let us know immediately. I explain to my patients that it’s inflammation in the lungs. If we can catch it early, then usually we can treat it easily. If I have a patient complaining of the symptoms, I tend to stop the drug and work it up with a CT of the chest.

If there is evidence of ILD, then depending on how significant the symptoms are, use steroids and keep the patient off therapy until you can get them back to a baseline again. Then, do you consider reattempting the drug? Do you have to look for another treatment option? However, [ILD] is not common. I don’t see it all the time. We do a lot of therapy [with trastuzumab deruxtecan] and it’s the same risk that you have with some of the other therapies we already have, such as everolimus (Afinitor). It’s important to be aware and educate the patients to be aware, too.

REFERENCE

LUNG, CONTINUED FROM PAGE 46

NSCLC, which is really exciting. There has been fast development with many other targets. We have drugs for BRAF, ROS1, NTRK, RET, and MET exon 14 skipping mutation and now [being developed for] KRAS; the list can keep going. The idea is that the more we look, the more we find these actionable driver mutations. When we find them, we can affect patients’ lives with many drugs. If you don’t look, you don’t know. If you look, will find these driver mutations in the patients’ tumors. There are so many different medications available [and ongoing] clinical trials for the rarer subsets so we can better understand [these patients]. That’s a big development.

Q: What are some recent advances in immunotherapy?

When I think about lung cancer education conferences—I’ve been doing them for a long time—it used to be that we would spend hours debating how to best treat patients with stage III lung cancer because we didn’t have much else to talk about. Then we started just talking about EGFR and then about all the other drivers.

Now when you go to conferences, [we discuss] immunotherapy for 2 days and then [spend] a half day on other things. That speaks to the importance of [immuno]therapy and also how much we still don’t understand. In a patient who has newly diagnosed disease with no driver mutation and high PD-L1 status, we can just give single-agent immunotherapy. If they have a high disease burden, we can give [immuno-therapy] with chemotherapy if we want them to have a [quick] response. If they have any level of PD-L1 expression and no driver mutation, we know they can get chemotherapy plus immunotherapy. We now have multiple drugs as options in that setting, and that has been really exciting.

Outside of the PD-L1 levels in the first-line setting, we don’t have great biomarkers. There have been a lot of discussions around tumor mutational burden [TMB]. Debates go back and forth between TMB being great and not so good; we don’t really know. We also know that single-agent pembrolizumab [Keytruda] doesn’t work for about half the patients, even if they have high PD-L1 expression. We don’t know why. Some of it has to do with the driver mutations, which is another reason those are so important to know, but that’s just a piece of it. There has to be something about the neoantigen and what the immune system recognizes about the tumor. However, we don’t know how to figure that out other than TMB, which isn’t great.

There is a lot to consider about the host, the host immunity, the microbiome, and so many other factors, but we’re just starting to understand it. We talk about it so much because, as much as it has tremendously helped a good percentage of patients, there is another huge percentage who are not necessarily helped by the checkpoint inhibitors. We need to understand that better.
Real-World Evidence Should Be Part of RCTs

by SARAH ALWARDT, PHD

AS CANCER TREATMENT SHIFTS from broad chemotherapy to highly personalized therapies, drug development in oncology is also evolving. There are currently some 71,000 oncology trials listed on ClinicalTrials.gov, with new studies being added every day. Although the trials may involve varied forms of disease or new modalities such as cell and gene therapies, all share 1 thing in common: They are competing with one another to recruit patients.

In the United States, fewer than 5% of adult patients with cancer enroll in clinical trials. This makes every patient extremely valuable.1 Sufficient enrollment is essential for successful completion of randomized controlled trials (RCTs) and for bringing new oncology drugs to patients sooner. However, we are unlikely to be able to recruit enough participants for many of these trials. In the oncology community, we must rethink how we populate trials and gather data for regulatory decisions.

RCTs remain the gold standard for evaluating the safety and efficacy of drugs, but the industry must identify alternative methods of gaining insight into treatment patterns and drug performance. The growth of personalized medicine and the complexity of the oncology treatment landscape offer an opportunity for the industry to expand the use of real-world evidence (RWE). We must consider expanding RCT eligibility to utilize RWE differently. This shouldn’t occur for the purposes of trial rescue, when recruitment and data capture have been inadequate. This use of RWE should involve planned studies with methodologies designed to capture data on the day-to-day usefulness of drugs. Examples of how RWE can be used in trials are below.

Real-world cohorts as part of RCTs. The use of pragmatic clinical trials, focusing on the correlation between treatments and outcomes in real-world clinical settings, has increased significantly over the past several years. Pragmatic trials offer the ability to test treatment options on realistic patient populations with fewer exclusions for common conditions that could affect outcomes in practice. The resulting data can be used for standalone analysis or as part of the RCT. For example, real-world data sources were used in a recent study to analyze the treatment patterns and duration of palbociclib (PAL; Ibrance), an oral inhibitor of cyclin-dependent kinase 4/6 inhibitor, with endocrine therapy (ET; aromatase inhibitor or fulvestrant) versus ET in men with metastatic breast cancer (mBC). The study used a retrospective analyses of pharmacy, medical claims, and other data and arrived at the conclusion that men with mBC derived clinical benefit from the addition of PAL to ET.2 According to investigators, given the challenges of conducting RCTs involving men with mBC, RWE data appear to be useful for assessing the benefit of novel therapies in this setting.

Synthetic control. Synthetic control cohorts must be embraced to support drug development and regulatory approval of breakthrough medicines designed to improve patient care. According to the FDA, synthetic control arms could help augment new clinical data by allowing biopharma company sponsors to reduce the number of patients assigned to the control arm in randomized trials or to conduct smaller randomized trials. The 2017 approval of avelumab (Bavencio) for Merkel cell carcinoma (MCC) marked the first-ever use of RWE for FDA approval. The approval was based on a phase II trial with only an active agent arm and a real-world retrospective analysis of patients with MCC treated with chemotherapy. The rarity of the disease made it impractical to conduct an RCT.3

Standard of care as control group. According to
the National Cancer Institute, standard of care is defined as treatment that experts agree is appropriate, accepted, and widely used. If a study is comparing new treatment options with a standard treatment that has not changed for years, why not use historic RWE as the control? If multiple biopharma companies are developing new drugs for the treatment of renal cell carcinoma, and each is conducting trials with nearly identical control groups, the possibility exists for all to draw data from the same control group. This may present some risk to the biopharma companies but could be a major boost for patients in the form of faster access to promising new therapies.

**FORMALIZE A 2-STEP REGULATORY APPROVAL PROCESS**

Under the FDA’s expanded access program, patients with an immediately life-threatening condition or serious disease may gain access to investigational drugs for treatment outside of clinical trials when no alternative therapy options are available. For patients who have exhausted approved options for treatment, participating in the expanded access program may be worth the risk of using an unapproved drug.

Although RWE is an extremely important tool to help address unmet patient needs, it is not a well-established regulatory pathway. The FDA has predicted that greater use of RWE will result in safety and efficacy information becoming available sooner and will help to further inform regulatory decisions. This is an opportunity to consider formalizing expanded access through the implementation of a 2-step approval process, similar to that used in Europe.

The European Medicines Agency (EMA) uses conditional marketing authorizations (CMA) to speed up access to medicines for patients with unmet medical needs. Between 2006 and 2016, CMAs were granted for 30 medicines that target such conditions as HIV infection, cancer, severe epilepsy in infants, and multidrug-resistant tuberculosis. Of these CMAs, 11 have been converted into full marketing authorizations, 2 have been withdrawn for commercial reasons, and the remainder remain valid CMAs. Companies that receive CMAs are required to conduct further studies to obtain complete data or meet other postauthorization requirements. According to the EMA, it takes an average of 4 years to generate the additional data needed to receive full marketing authorization.

In the United States, biopharma companies could receive conditional approval from the FDA on the basis of early-phase RCT data, such as a completed phase II trial data or initial data from a phase III trial. Once conditional approval is granted, the sponsor would be required to complete more comprehensive trials for final approval of a new drug application (NDA) or supplemental NDA.

RWE can be analyzed and compared with outcomes expected under an RCT by using a pragmatic trial and monitoring patients longitudinally for 12 to 18 months. The FDA has signaled openness to this approach in its recent RWE framework and in the expansion of its RCT DUPLICATE demonstration project, designed to use RWE to attempt to replicate the results of 30 RCTs. The goal of this project is to help inform the FDA’s standards for using RWE in regulatory decision-making and to identify when and where RWE can provide estimates of treatment safety and efficacy.

**RETHINKING RCT ELIGIBILITY**

Clinical trial recruitment is sometimes challenging, and cancer trials can be closed prematurely because of poor accrual. Additionally, significant disparities exist in RCT participation. Clinical trial populations tend to encompass younger, healthier patient populations than are found in the real world, with limited ethnic and gender diversity. Although RCTs remain the gold standard for the assessment of safety and efficacy, clinical trials alone will not be sufficient to accelerate desperately needed advances in cancer care. RWE will continue to play an important role in drug development and testing by providing critical information about how new treatments perform in real clinical settings. As the FDA finalizes its guidelines for how and when industry can use RWE to support regulatory decisions, we must also work in parallel to expand RCT eligibility to include real-world patient populations. This will improve our ability to recruit patients and complete RCTs as well as bring new oncology drugs to market sooner.

For a full list of references, see the article at OncLive.com.
FIGHT ON

with ONIVYDE®

The first and only FDA-approved treatment, in combination with 5-FU/LV, for metastatic pancreatic cancer after gemcitabine-based therapy, proven to extend overall survival (OS)¹

INDICATION
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late-onset diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

WARNINGS AND PRECAUTIONS

Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE + 5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE + 5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset ≥24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE + 5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE + 5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

ADVERSE REACTIONS

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%), late diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%], fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%,

Please see additional Important Safety Information throughout and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.
ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST-GEMCITABINE METASTATIC PANCREATIC CANCER

FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE1

- Proven in combination with 5-FU/LV in NAPOLI-1—the largest phase 3 trial1 in patients with metastatic pancreatic cancer with disease progression after gemcitabine-based therapy.3,4

**References:**

For more information, visit ONIVYDEinfo.com

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* Liposomal irinotecan + 5-FU/LV is the only Category 1 National Comprehensive Cancer Network® (NCCN®) chemotherapy recommendation for patients with post-gemcitabine metastatic pancreatic cancer with good performance status and disease progression.1 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.

1 NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m² every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were progression-free survival and objective response rate.1,4

- **DRUG INTERACTIONS**

Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme-inducing therapies ≥2 weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy.

- **USE IN SPECIFIC POPULATIONS**

**Pregnancy and Reproductive Potential**

Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

**Lactation**

Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

**Pediatric**

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

- **DOSE AND ADMINISTRATION**

The recommended dose of ONIVYDE is 70 mg/m² intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD. Do not substitute ONIVYDE for other drugs containing irinotecan HCL.

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ONIVYDE® (irinotecan liposome injection) for intravenous use
Initial U.S. Approval: 1996

BRIEF SUMMARY: refer to full Prescribing Information for complete product information.

1. INDICATIONS AND USAGE
ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas (see Clinical Studies, 14).

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE®. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. (see Dosing and Administration 2.2, 5.1)

Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Reduce loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity. (see Dosing and Administration 2.2, see Warnings and Precautions 5.2)

4 CONTRAINDICATIONS
ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Neutropenia: ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count [ANC] is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosage and Administration, 2.2).

5.2 Severe Diarrhea: ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) (see Cholinergic Reactions, 6.1). An individual patient may experience both early- and late-onset diarrhea. In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose (see Dosage and Administration, 2.2).

5.3 Intestinal Lymph Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1).

6 ADVERSE REACTIONS
The following adverse drug reactions are discussed in greater detail in other sections of the label:

• Severe Neutropenia (see Warnings and Precautions, 5.1; Boxed Warning)
• Severe Diarrhea (see Warnings and Precautions, 5.2; Boxed Warning)
• Intestinal Lymph Disease (see Warnings and Precautions, 5.3)
• Severe Hypersensitivity Reactions (see Warnings and Precautions, 5.4)

6.1 Clinical Trials Experience
The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 weeks rest (5-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/5-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
An individual patient may experience both early- and late-onset diarrhea. 

Treatment of patients with metastatic adenocarcinoma of the pancreas progressing following gemcitabine-based therapy.

Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically indicated). Withhold ONIVYDE® if the absolute neutrophil count is below 1500/mm³ or thrombocytopenia.

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifampentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

7.2 Strong CYP3A4 or UGT1A1 Inhibitors: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE® with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, neflavin, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥21 week prior to starting ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy, Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

8.2 Lactation, Risk Summary: There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk (see Data in the full Prescribing Information).

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

8.3 Females and Males of Reproductive Potential, Contraception, Females: ONIVYDE® 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 ONIVYDE® and for 1 month after the final dose. Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE® and for 4 months after the final dose (see Nonclinical Toxicology, 13.1).

8.4 Pediatric Use: Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

8.5 Geriatric Use: Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/5-FU/LV in Study 1, 49% were ≥65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE®.

Table 2: Adverse Reactions with Higher Incidence (≥25% Difference for Grades 1–4 or ≥22% Difference for Grades 3 and 4) in the ONIVYDE®/5-FU/LV Arm

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE®/5-FU/LV n=117</th>
<th>5-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4 (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea‡</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis◆</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Intravenous catheter-related infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Dehydration</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

*NCI CTCAE v4.0.
†Early diarrhea: onset ≤24 hours of ONIVYDE® administration.
‡Late diarrhea: onset >1 day after ONIVYDE® administration.
§Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
◆Includes febrile neutropenia.

Cholinergic Reactions: ONIVYDE® can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE®-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE® administration, were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV.

The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥25% difference Grades 1–4 [any] or ≥22% difference Grades 3–4 [severe] according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/5-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. Hematologic: anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). Hepatic: increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hyperbilirubinemia (any 43%, 30%; severe 2%, 0%). Metabolic: hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypercalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hypernatremia (any 27%, 12%; severe 5%, 3%). Renal: increased creatinine (any 18%, 13%; severe 0%, 0%).
Hematopoietic Stem Cell Transplant: A Viable Option for Older Patients With AML

by MARK B. JUCKETT, MD

ACUTE MYELOID LEUKEMIA (AML) is diagnosed at a median age of 68 years, well beyond an age in which intensive therapy and allogeneic hematopoietic stem cell transplantation (HSCT) is typically considered an option. This approach is not easily applied to patients 60 years and older because of limitations caused by comorbidities, performance status, and frailty. In addition, older patients (here defined as those 60 years and older) tend to have disease that is more aggressive, harbors high-risk cytogenetics or molecular lesions (ie, p53 mutations), and is less sensitive to cytotoxic chemotherapy.

Fortunately, the therapeutic landscape for older patients with AML is changing and cure remains a viable goal for many individuals. Several new therapies have been approved by the FDA since 2016 and HSCT is feasible for a growing subset of older patients given the availability of less-toxic preparative regimens, increased donor options, and novel approaches to reduce the risk of graft-versus-host disease (GVHD). The challenge in caring for older patients is developing a risk-adapted strategy that best meets the patients’ identified goals and accounts for a realistic assessment of HSCT suitability.

New agents approved for the treatment of AML include liposomal daunorubicin/cytarabine (Vyxeos) and several targeted agents, includingenasidenib (Idhifa), ivosidenib (Tibsovo), midostaurin (Rydapt), gilteritinib (Xospata), glasdegib (Daurismo), and venetoclax (Venclexta).

Although the new agents are promising and better tolerated compared with traditional 7 + 3 induction chemotherapy, they are not expected to lead to long-term remission, and HSCT remains the only option with cure as a realistic goal. If an older patient is a possible candidate for HSCT, the best initial treatment will have the features of maximizing the chance for a deep remission, while sparing the patient the risk of morbidity due to chemotherapy-associated adverse events and neutropenic-related complications.

Although we have no comparative studies between the recently approved novel agents to make evidence-based decisions, the options most likely to lead to complete remissions are midostaurin with 7 + 3 for patients with FLT3-positive AML, liposomal daunorubicin/cytarabine for AML with myelodysplastic syndrome-like cytogenetic changes, and the combination of venetoclax and a hypomethylating agent.

Each of these approaches appears to have advantages over traditional induction and may improve outcome following HSCT.

USING GERIATRIC ASSESSMENT TO DETERMINE CANDIDACY FOR HSCT

Although debate remains over the particular details of eligibility, a geriatric assessment (GA) of function, frailty, comorbidities, mental health, nutrition, and inflammation appears to be more important than chronological age. The hematopoietic comorbidity index has been validated as a tool to predict nonrelapse mortality after HSCT in patients of all ages and also predicts survival following induction at the time of initial AML diagnosis.1,2

An assessment of frailty among older patients using Lawton’s Instrumental Activities of Daily Living demonstrated a 2.38-fold increase in mortality risk after HSCT3 among those with impairment.
The promise of a comprehensive GA in predicting outcomes among older patients will be tested in BMT CTN Protocol 1704 (NCT03992352), which seeks to collect data on 1,100 patients 60 years and older undergoing HSCT. Enrolled patients will undergo a comprehensive GA including inflammatory biomarkers before undergoing HSCT and the association of outcome with specific components of the GA determined. Once completed, the results will help physicians provide guidance to older patients considering HSCT versus nontransplant therapies for AML treatment (FIGURE 4).

NONRELAPSE MORTALITY REMAINS A CONCERN

The older patient population presents novel challenges to physicians because of the increased nonrelapse mortality associated with intense, myeloablative regimens. A variety of reduced-intensity regimens have been developed, and there continues to be investigation into how “reduced intensity” a regimen can be to optimize the chance of long-term survival.

A randomized comparison of myeloablative versus reduced-intensity regimens showed a relapse-free survival at 18 months of 67.8% versus 47.3%, respectively among patients aged younger than 65 years indicating the importance of regimen intensity.5

Multiple studies have demonstrated rising relapse risk associated with less myelosuppressive regimens. An important principle is to match the intensity of the regimen to the patient’s predicted tolerance, given knowledge about other risk factors for nonrelapse mortality. The physician must tailor the choice of regimen within a desired window of safety, taking into account the patient’s unique features.

GVHD is the most important long-term risk and responsible for impairing quality of life and increasing morbidity following HSCT. A recent BMT CTN clinical trial identified posttransplant cyclophosphamide, tacrolimus, and mycophenolate mofetil as the most promising novel approach to reducing GVHD risk and improving survival without relapse or GVHD after reduced-intensity HSCT. BMT CTN 1703 (NCT03959241) will compare the long-term GVHD relapse-free survival among patients receiving posttransplant cyclophosphamide/tacrolimus/mycophenolate mofetil versus conventional tacrolimus and methotrexate. The study will include measures of quality of life to further elucidate the optimal approach to GVHD prophylaxis after reduced-intensity conditioning and the results will establish a new standard for GVHD prevention.

FUTURE DIRECTIONS

HSCT is increasingly an option for older patients with AML as preparative regimens, donor options, and novel approaches to prevent GVHD have expanded. A variety of so-called reduced-intensity conditioning regimens have been developed and used for HSCT among patients into their mid- to late-70s. A recent retrospective study compared patients with AML aged 60 to 75 years who underwent reduced-intensity conditioning transplantation with those eligible to be treated with consolidation chemotherapy on cooperative groups’ trials.6 Among patients in first complete remission, survival within the first 9 months was superior among the patients treated with chemotherapy, although beyond 9 months, those treated with HSCT fared better. At 5 years, 29% versus 13.8% of patients were alive after HSCT versus undergoing chemotherapy, respectively.

A recent prospective study of reduced-intensity HSCT among patients 60 years and older demonstrated disease-free and overall survival at 2 years of 42% and 48%, respectively.7 Although much remains to be learned regarding patient and donor characteristics, GVHD prevention, and post-HSCT management to improve outcome, HSCT is a viable option for many older patients with AML.

REFERENCES


Immunotherapy Biomarker Testing Depends on Tumor Type

by AUDREY STERNBERG

SINCE THE FIRST TUMOR-AGNOSTIC immunotherapy was approved in 2017, questions about optimal procedures for biomarker testing have become more pressing. A Working Group of the European Society for Medical Oncology (ESMO) has determined that a decision tree on the sequential use of different tests in immunotherapy decision-making cannot be a general one for all cancers but should be designed on the basis of the specific tumor type.

Through a new published recommendation, the ESMO Working Group has set a standard for the definition of microsatellite instability (MSI)/mismatch repair deficient (dMMR), tumor mutational burden (TMB), and PD-L1 expression, as well as the relationships among these tests.1

MSI has been an FDA-indicated biomarker for immunotherapy since 2017, when the PD-1 inhibitor pembrolizumab (Keytruda) was approved for patients with solid tumors found to be dMMR or MSI high (MSI-H).2 Other approvals since then, such as for the combination of ipilimumab (Yervoy) and nivolumab (Opdivo) in patients with MSI-H/dMMR metastatic colorectal cancer,3 have established the relevance of cancer therapies directed at this biomarker specifically rather than tumor histology alone.

“MSI is a diagnostic test for screening for the broad spectrum of Lynch syndrome–associated cancers, but it is also a prognostic test for gastrointestinal cancers and a predictive marker for immunotherapy,” Aldo Scarpa, MD, PhD, director of the Applied Research on Cancer–Network Research Centre for Applied Research on Cancer and chair of the Department of Pathology and Diagnostics at the University and Hospital Trust of Verona, Italy, said during a presentation of the working group’s data at the ESMO Immunology Oncology Congress 2019, held December 11 to 14, 2019, in Geneva, Switzerland.4

Tumors that are dMMR accumulate mutations in regions of DNA called microsatellites, which are prone to mismatch errors; the result is the condition known as MSI. A hallmark of Lynch syndrome, MSI can occur in a variety of cancers, including colorectal, endometrial, and gastric.

To promote the use of clear and consistent terminology in future research, the collaborative group established standardized definitions for MSI-related terms from a systematic review of 18 articles related to MSI. These definitions are outlined in TABLE 1.1,4

TABLE 1. Definitions of MSI and MSI-Related Terms1,4

<table>
<thead>
<tr>
<th>Microsatellites</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Repetitive DNA sequences that are distributed along the genome, in both coding and noncoding regions</td>
</tr>
<tr>
<td>• Composed of repeats ranging from 1 to 6 bases</td>
</tr>
<tr>
<td>• Highly polymorphic among different patients but typically the same length in the patient’s germline DNA and in the somatic DNA of the tumor</td>
</tr>
<tr>
<td>• Repetitive nature renders them sensitive to mismatch errors occurring during DNA replication or iatrogenic damage.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DNA mismatch repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highly conserved mechanism to restore DNA integrity after the occurrence of mismatch errors, including single-base mismatches and short insertions or deletions</td>
</tr>
<tr>
<td>• Four genes play a role in this process: MLH1, MSH2, MSH6, and PMS2</td>
</tr>
<tr>
<td>• The proteins encoded by these genes function as the heterodimers MLH1-PMS2 and MSH2-MSH6.</td>
</tr>
<tr>
<td>• Inactivation of 1 of these genes, via either germline or somatic mutation, can result in dMMR.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microsatellite instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Condition of genetic hypermutability resulting from dMMR</td>
</tr>
<tr>
<td>• Characterized by clustering of mutations in microsatellites typically consisting of repeat-length alterations</td>
</tr>
<tr>
<td>• MSI presence represents phenotypic evidence of abnormal MMR function.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microsatellite instability/deficient mismatch repair tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tumor that accumulates thousands of mutations, particularly clustered in microsatellites and consisting of repeat-length alterations, resulting in MSI</td>
</tr>
<tr>
<td>• MSI is a marker of dMMR and characterizes a hypermutable state of cells.</td>
</tr>
</tbody>
</table>

dMMR indicates deficient mismatch repair; MMIR, mismatch repair; MSI, microsatellite instability.

TESTING FOR MSI

To better understand the rationale behind testing methodologies, the collaborative group examined the mechanisms underlying DNA mismatch repair (MMR) across different solid tumors.

The MMR proteins form heterodimers consisting of MLH1 and PMS2 or MSH2 and MSH6. MLH1 and MSH2 are considered the “obligatory partners” in these protein pairs; alterations in them interfere with dimerization and result in proteolytic degradation of both proteins in the heterodimer. However, the same is not necessarily true of the “secondary partners,” PMS2 and MSH6, because other proteins may substitute for them in the heterodimer. Therefore, functional heterodimers may be present despite PMS2 or MSH6 mutations.

For the spectrum of cancers associated with Lynch syndrome, immunohistochemistry (IHC) of all 4 MMR proteins is the first line of testing. Subsequently, MSI-polymerase chain reaction (PCR) molecular testing of specific microsatellite loci is indicated for cases in which IHC results are indeterminate, such as the loss of only 1 heterodimer subunit.

“When you have an alteration of a secondary partner, you may have an immunohistochemistry [result that] is not informative because you do not have the loss of both partners,” Scarpa said. “This is because PMS2 may be substituted for PMS1 or MLH3, and MSH6 may be substituted for MSH3. Alterations of secondary proteins may be compensated by other partners, and so the machinery is working.”

Normal cells with increased turnover—such as mucosal cells, lymphocytes, and stromal cells—must serve as an internal positive control for IHC testing. Determinant IHC findings include positive results, in which tumor and control cells exhibit nuclear staining of comparable intensity, and negative results, in which control cells have nuclear staining but tumor cells do not. However, cases with negative staining of controls or weaker staining of tumor cells compared with controls require verification by MSI-PCR, which has the highest specificity and sensitivity.

For cancers not associated with Lynch syndrome, the consensus group touted the...
advantages of next-generation sequencing (NGS), which can couple analyses of MSI and TMB (Table 2). In a study analyzing sequence data from 5930 cancer samples, investigators found MSI-H tumors in 14 of the 18 cancer types studied, with incidences ranging from about 30% for endometrial cancer to <1% for thyroid carcinoma. In a similar study, MSI was detected in 27 of 39 cancer types analyzed, mostly at low proportions; only 4 types had an MSI-H frequency >5%.

“We cannot imagine [developing] these tests to analyze all these cases unless we use NGS,” Scarpa said. “In [cancers of] other organs outside Lynch syndrome, we do not understand how to work with immunohistochemistry [to determine] the real partners of MMR. With NGS, you can analyze several dozen genes to get information about mutations, loss, amplifications, and copy-number alterations. Moreover, you have the mutational spectrum, which [refers to] the types of combinations of mutations that may happen through different mechanisms.”

RELATING MSI TO TMB AND PD-L1 EXPRESSION

From the 18 articles selected for systematic review, the collaborative group attempted to identify associations with immunotherapy response among 3 biomarkers: high TMB, PD-L1 expression on tumor cells, and MSI. In total, 4186 patients were positive for at least 1 of the biomarkers, with the simultaneous presence of all 3 in 2.9% of cases. Significantly higher (P < .05) rates of positivity for all 3 biomarkers were observed in patients with colorectal and esophagogastric adenocarcinomas, at 12.8% and 14.6%, respectively.

Notably, the majority of patients with colorectal cancer who had MSI also had high TMB, and vice versa. Positivity for both biomarkers (but not PD-L1) accounted for 31.4% of patients, indicating a high concordance between the 2 indices. Patients with MSI alone or high TMB alone accounted for just 1.7% and 8.7%, respectively, of patients with colorectal tumors. Patients with PD-L1 expression alone made up 43.6% of the population.

Investigators observed similar concordance in patients with esophagogastric adenocarcinomas, with 13.1% of tumors exhibiting both high TMB and MSI (but not PD-L1). High TMB or MSI alone was observed in 3.7% and 5.1% of patients, respectively. In total, 14.6% of patients in this population expressed all 3 biomarkers simultaneously.

In endometrial cancer, high TMB was almost always accompanied by MSI; however, the inverse correlation was not observed. Among patients with this cancer, 25.8% expressed both biomarkers (but not PD-L1), 19.9% had MSI only, and 4.9% had high TMB only. In 12.8% of patients, the tumors expressed all 3 biomarkers.

MSI was absent in melanoma cases and present in only a small number of cases of non–small cell lung cancers.

In all cancer types studied, PD-L1 expression was not found to necessarily co-occur with other biomarkers, and it was the most frequently occurring biomarker in most tumor types.

PRACTICAL APPLICATIONS

The consensus group concluded that clinicians should perform first-line MSI testing using IHC for all 4 MMR-associated proteins for the cancer types frequently associated with Lynch syndrome, which include endometrial, intestinal, gastric, and ovarian cancers, as well as esophageal adenocarcinoma and glioblastoma. In cases of indeterminate IHC results, second-line testing should be performed using a molecularly based assay, with MSI-PCR as the preferred method. For rare cancer types and those not associated with Lynch syndrome, MSI testing should be performed using NGS. The group also noted that although correlations with TMB and PD-L1 may be useful for future prognostication, MSI-H tumors do not need to express either of these biomarkers to necessitate use of immunotherapy.

Ongoing research advancing the role of MSI as a biomarker for immunotherapy responses and clarifying its relationship with other biomarkers will continue to elucidate the role of MSI in the treatment of solid tumors.

Table 2. Recommendations for MSI Testing Methods in Different Cancer Types

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>MSI Prevalence (all stages)</th>
<th>Specific MSI-associated Histotype, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>17%</td>
<td>Medullary, mucinous, poorly differentiated neuroendocrine</td>
</tr>
<tr>
<td>Endometrial</td>
<td>20%</td>
<td>Lower uterine segment-located, undifferentiated/de-differentiated, mixed morphology, tumors showing high levels of tumor-infiltrating lymphocytes/lymphoid stroma</td>
</tr>
<tr>
<td>Gastric-esophageal</td>
<td>13%</td>
<td>Adenocarcinoma (MSI up to 39% in case of carcinoma with lymphoid stroma and absent in esophageal squamous cell carcinoma)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>8.3%</td>
<td>Including duodenum and ampulla of Vater</td>
</tr>
<tr>
<td>Ovarian</td>
<td>3.5%-10%</td>
<td>Endometrioid, clear cell</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>6%-13%</td>
<td></td>
</tr>
</tbody>
</table>

**Testing using IHC and MSI-PCR or NGS**

| Unknown primary              | 1.8%                        |
| Cervical                    | 4%                          |
| Extrahepatic bile duct      | 3.4%                        |
| Pancreatic                  | 1%-7%                       | Medullary, IPMN-associated, periampullary (when the origin from ampulla, terminal bile duct, or pancreatic duct is uncertain) |
| Prostate                    | 3%                          |
| Non–small cell lung cancer  | <1%                         |
| Head and neck               | <1%                         |
| Melanoma                    | NS                          | 1% uveal melanoma |
| Sarcomas                    | 2%                          | Uterine, peritoneal, and retroperitoneal |
| Anal                         | NS                          |
| Kidney                       | NS                          |

IHC indicates immunohistochemistry; IPMN, intraductal papillary mucinous neoplasm; MSI, microsatellite instability; MSI-PCR, microsatellite instability-polymerase chain reaction; NGS, next-generation sequencing; NS, no significant evidence.

*Belong to the Lynch Syndrome spectrum. NGS is indicated for stage IV cancers, which have a lower MSI prevalence than earlier stage disease.

*Do not belong to the Lynch Syndrome spectrum with low prevalence of MSI and little data available on the reliability of IHC and MSI-PCR.

For a full list of references, see the article at OncLive.com.
Indications and Usage
Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

Important Safety Information
- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10⁹/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some...
Significantly more patients receiving Jakafi achieved the composite primary* and key secondary end points2,3†

Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

Patients Achieving Complete Hematologic Remission**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Jakafi (n = 110)</th>
<th>BAT (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24%</td>
<td>(n = 26)</td>
<td>(n = 9)</td>
</tr>
<tr>
<td>P = 0.0016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** The RESPONSE (Randomized study of Efficacy and Safety in POlycythemia vera with JAK Inhibitor ruxolitinib veSuS bEst available care) trial was a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with BAT in 222 patients with polycythemia vera. All patients were required to demonstrate Hct control between 40% and 45% prior to randomization. BAT included hydroxyurea (60%), interferon/polyethylene interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). Patients enrolled in the study had been diagnosed with polycythemia vera for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy for Hct control, and exhibited splenomegaly. After week 32, patients were able to cross over to Jakafi treatment. A durability analysis was performed at week 80 in the original Jakafi arm.

Durable response at week 802

- 19 of 25 patients (76%) who achieved a primary response at week 32 in the Jakafi arm maintained their response
- 51 of 66 patients (77%) who achieved Hct control at week 32 in the Jakafi arm maintained their response
- 43 of 44 patients (98%) who achieved a ≥35% spleen volume reduction at week 32 in the Jakafi arm maintained their response
- 15 of 26 patients (58%) who achieved complete hematologic remission at week 32 in the Jakafi arm maintained their response

Durable count control

- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for two weeks after the final dose.

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

To learn more about intervening with Jakafi, visit HCP.Jakafi.com.

Infection
see Adverse Reactions (6.1) in Full Prescribing Information. Platelet transfusions may be necessary [see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information]. Risk of Infection See Section 1.4 in the package insert. Infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. Progressive, Multifocal Leukoencephalopathy Progression of multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [see Adverse Reactions (6.1) in Full Prescribing Information]. Hepatitis B Viraemia Jakafi B viral load (HBV DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infection taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Symptom Exacerbation Following Interuption or Discontinuation of Treatment with Jakafi Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to abruptly or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [see Dosage and Administration (2.6) in Full Prescribing Information], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. Non-Melanoma Skin Cancer Non-Melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. Lipid Elevations Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. ADVANCE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombotic Microangiopathy, Anemia and Neutropenia [see Warnings and Precautions (5.1) in Full Prescribing Information] • Risk of Infection [see Warnings and Precautions (5.2) in Full Prescribing Information] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see Warnings and Precautions (5.3) in Full Prescribing Information] • Non-Melanoma Skin Cancer [see Warnings and Precautions (5.5) in Full Prescribing Information]. Clinical Trials Experience in Myelofibrosis 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 clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 17 patients in two clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25% of patients, respectively, required a dose reduction before the starting dose within the first 4 weeks of therapy. Table 1: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Double-blind, Placebo-controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
</tbody>
</table>
| 25% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25% of patients, respectively, required a dose reduction before the starting dose within the first 4 weeks of therapy. Table 1: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Double-blind, Placebo-controlled Study During Randomized Treatment

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</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
</tbody>
</table>

• 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alamine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in asparagine transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 4 or 3 cholesterol elevations Clinical Trial Experience in Polycythemia Vera In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see Clinical Studies (14.2) in Full Prescribing Information]. The most frequent adverse drug reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
</tbody>
</table>

![Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Double-blind, Placebo-controlled Study](image-url)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Cough</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
</tbody>
</table>

![Table 3: Polycythemia Vera: Treatment Emergent Adverse Events](image-url)
**Table 3 Continued**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypochromatemia</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Elevated AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertrichycardia</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

- *Presented are worst Grade values regardless of baseline
- *National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

**Clinical Trial Experience in Acute Graft-Versus-Host Disease**

In a single-arm, open-label study, 71 adults (age 18-73 years) were treated with Jakafi for acute GvHD failing treatment with steroids with or without other immunosuppressive drugs [see Clinical Studies (14.3) in Full Prescribing Information]. The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

**Table 5: Acute Graft Versus Host Disease: Nonhematological Adverse Reactions Occurring in ≥15% of Patients in the Open-Label, Single-Cohort Study**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=71)</th>
<th>Best Available Therapy (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td>55</td>
<td>41</td>
</tr>
<tr>
<td>Edema</td>
<td>51</td>
<td>13</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Viral infections</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

- *Selected laboratory abnormalities are listed in Table 16 below
- *National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

**Selected laboratory abnormalities during treatment with Jakafi are shown in Table 6.**

**Table 6: Acute Graft Versus Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single Cohort Study**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=71)</th>
<th>Best Available Therapy (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>75</td>
<td>45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58</td>
<td>40</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>Hypertrichycardia</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

- *National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

**Drug Interactions**

**Flucytosine**

Concomitant administration of Jakafi with flucytosine doses greater than 200 mg daily may increase rutinolubin exposure due to inhibition of both the CYP3A4 and CYP2C3 metabolic pathways [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with flucytosin doses of greater than 200 mg daily in patients with acute graft (see Dosage and Administration (2.4) in Full Prescribing Information). See Strong CYP3A4 inhibitors Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases rutinolubin exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [see Dosage and Administration (2.4) in Full Prescribing Information]. In patients with acute GvHD, reduce Jakafi dose as recommended only when coadministered with ketoconazole, and monitor blood counts more frequently for toxicity and adjust the dose if necessary when coadministered with fluconazole, and monitor blood counts more frequently for toxicity and adjust the dose if necessary when coadministered with ketoconazole. [see Dosage and Administration (2.4) in Full Prescribing Information]. 

**Pathogenic**

In pathogenic organisms, JAKs are required for signal transduction and cytokine expression. JAK inhibitors block JAK signaling and reduce cytokine expression, which suppresses the immune response. Jakafi has demonstrated a favorable safety profile in clinical trials.

**Dosage and Administration**

**2.4** in Full Prescribing Information.

The dosages of Jakafi were determined based on the overall risk-benefit determination. For Full Prescribing Information, see Warnings and Precautions (5.4). Discontinuation for toxicity was based on the overall risk-benefit determination. For Full Prescribing Information, see Dosage and Administration (2.4). Clinical Pharmacology (12.3) in Full Prescribing Information. Additional analysis showed the presence of rutinolubin and several of its metabolites in milk, all at levels higher than those in maternal plasma. Pediatric Use The safety and effectiveness of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients have not been established. The safety and effectiveness of Jakafi for treatment of steroid-refractory acute graft-versus-host disease (GvHD) have been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory acute GvHD is supported by evidence from an adequate and well-controlled trial of Jakafi in adults [see Clinical Studies (14.3) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to <12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 25, 39, or 50 mg/m² twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than one single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximum tolerated dose was not reached, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults. Juvenile-Antibody Toxicity Data Administration of rutinolubin to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

**Geriatric Use**

The total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these older and younger patients. Clinical studies of Jakafi in patients with acute GvHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

**Renal Impairment**

Total exposure of rutinolubin and its active metabolites increased with moderate (Ccr 30-59 mL/min) and severe (Ccr 15-29 mL/min) renal impairment, and ESRD on dialysis [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Reduce Jakafi dose as recommended [see Dosage and Administration (2.5) in Full Prescribing Information].

**Hepatic Impairment**

Exposure of rutinolubin increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Reduce Jakafi dose as recommended in patients with MR or PV and any hepatic impairment [see Dosage and Administration (2.5) in Full Prescribing Information]. Monitor blood counts more frequently for toxicity and consider 5 mg once daily for patients with Stage 3 or 4 liver G1 to see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information.

**OVERDOSAGE**

There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.
New Era of CDK Targeting Gets Rolling

by JANE DE LARTIGUE, PHD

IN THE ONCOLOGY SPHERE, 2 members of the cyclin-dependent kinase (CDK) family have long stood out from the crowd. Serving as gatekeepers at the entry to the cell cycle, CDK4 and CDK6 make ideal therapeutic targets to block the unchecked proliferation that is a hallmark of cancer cells. Case in point: The FDA has approved 3 CDK4/6-targeted drugs for the treatment of a specific subtype of breast cancer.1

Yet the CDK family encompasses 20 proteins2 with important functions beyond cell cycle regulation.3 Growing appreciation of the role of CDKs in transcriptional regulation is fueling renewed interest in developing inhibitors of other CDKs, particularly CDK7 and CDK9.

A better understanding of the role of transcriptional CDKs has refocused the development of drugs such as alvocidib, which may have found a niche in several hematologic malignancies in combination therapies. The drug is an intravenous (IV) inhibitor of multiple CDKs.

Meanwhile, oral inhibitors of transcriptional CDKs also demonstrate promise in hematologic malignancies. Zotiraciclib (TG02), the most potent inhibitor of CDK9 developed to date, has received an orphan drug designation from the FDA for glioma therapy, based on positive phase I data.4

Efforts to recapitulate the success of CDK4/6 inhibitors are also driving the pursuit of more selective inhibitors. Promising preclinical data propelled several drugs into early stages of clinical testing amid a potential new era of CDK-targeted therapy (TABLE).

GUARDIANS OF THE CELL CYCLE

CDK proteins derive their importance as an anticancer target from the vital role they play in the cell cycle. The cell cycle is divided into 5 phases: growth (G1 and G2 phases), DNA replication (S), mitosis (M), and quiescence (G0). Mitogenic stimulation triggers quiescent cells to enter the cell cycle, and progression from one phase to the next is tightly controlled by numerous proteins to ensure each step occurs at the appropriate time (FIGURE).1,3

Among these proteins are the CDKs, a family of 20 serine/threonine kinases2 that are fully functional only when bound to a cyclin.1,3,5

CDK activity is also regulated by other activating and inhibitory proteins, including CDK-activating kinases (CAKs) and the INK4 and CIP/KIP families of cyclin-dependent kinase inhibitors (CKIs), respectively.5

Mitogens trigger intracellular signaling cascades, most notably involving the MAPK pathway, that ultimately induce the transcription of D-type cyclins, which form active complexes with CDK4 and CDK6. These CDK4/6-cyclin D complexes drive phosphorylation of the retinoblastoma (RB) protein, leading to the transcription of genes encoding proteins that promote the transition from G1 to S phase, such as cyclin E. Progression to S phase represents a particularly important cell cycle checkpoint—the restriction point—whereupon the cell fully commits to entering the cell cycle.1,3,5

As the cell cycle progresses, the CDK2-cyclin E complex regulates DNA synthesis during S phase. Then, cyclin E levels decrease concurrently with an increase in the levels of cyclin A, which becomes the main cyclin bound to CDK2 to terminate S phase. Subsequently, CDK1 binds to cyclin A to trigger progression into G2 phase and to cyclin B to facilitate the expression of genes involved in mitosis. Cyclin B is degraded at the end of mitosis, switching off CDK1 activity. As RB is dephosphorylated, the cell enters G0 once again.1,3

Deregulation of the cell cycle is a key hallmark of cancer. Mutations in the genes encoding CDKs are rare in cancer, but gene amplification and protein overexpression of CDKs or their cyclin partners are common. Most often, aberrant activation of CDKs occurs indirectly, via alterations in the proteins that regulate them.1,3,7

Amplification of the genes encoding cyclins is particularly common across cancer types and, in fact, is one of the most common alterations in cancer in general. CCND1, which encodes cyclin D1, is amplified at rates of 15% to 40% in many common cancers, such as breast and lung cancers.5,8 Alterations in other CDK regulatory proteins are also commonly observed across the spectrum of cancers.9,10

As a result of their key role in oncogenesis and their status as readily druggable kinases, CDKs have long been recognized as prime targets for therapeutic intervention. The first CDK inhibitor to enter clinical trials was alvocidib (also called flavopiridol). Despite strong preclinical efficacy, alvocidib and other multitargeted CDK inhibitors demonstrated disappointing single-agent activity and were often hindered by low therapeutic indexes and significant toxicity.1,3
The field underwent a renaissance with the development of highly selective inhibitors of CDK4/6; the most significant leap forward came in 2009, when the front-runner, palbociclib (Ibrance), was shown to have activity in estrogen receptor (ER)–positive breast cancer cell lines. Combined inhibition of CDK4/6 and ER signaling was particularly effective, likely because of documented interplay between the cyclin D-CDK4/6 pathway and ER activation.11

Palbociclib and 2 other CDK4/6 inhibitors, abemaciclib (Verzenio) and ribociclib (Kisqali), are now approved by the FDA in combination with standard-of-care hormone therapies to treat hormone receptor–positive, HER2-negative, advanced or metastatic breast cancer.1,3

**BEYOND CDK4/6**

Alvocidib is an inhibitor of CDks 1, 2, 4, and 9; and its antitumor effects were initially attributed to its inhibition of cell cycle CDKs. However, it most potently inhibits CDK9, which is not directly involved in regulation of the cell cycle, suggesting that its mechanism of action is related to another important function of CDKs—the regulation of transcription.12

RNA polymerase II is a multiprotein complex that plays a central role in the transcription of all protein-coding genes. The largest subunit of this complex is the RPB1 protein, which contains a carboxy-terminal domain (CTD) that is recognized by many kinases, phosphatases, and other posttranslational modifiers. CDKs, particularly CDK7 and CDK9, are among the kinases that phosphorylate the CTD at distinct serine residues.3,13

Transcriptional CDKs differ from their cell cycle counterparts. They typically form part of larger multiprotein complexes; CDK7 and cyclin H make up part of the 10-subunit general transcription factor (TFIIH) complex, whereas CDK9 and cyclin T form the catalytic subunit of the positive transcription elongation factor b (P-TEFb) complex. Another important mediator of transcription is CDK8 and its parologue CDK19, which, along with cyclin C, are reversibly associated with the Mediator complex, a global regulator of RNA polymerase II activity.3,13

Historically, CDK7 (through the TFIIH complex) thought to primarily control the initiation of transcription. CDK9 and the P-TEFb complex, on the other hand, were believed to function in transcriptional elongation through phosphorylation of serine 2. CDK8 was thought to repress transcription by preventing the Mediator complex from binding to RNA polymerase II.3,13

CDK involvement in transcription is likely much more complex than that; however, evidence has emerged for significant cross talk between transcriptional CDKs, context-dependent roles for each complex, and a potentially transcription-promoting role for CDK8. Furthermore, the identification of 2 additional transcriptional CDKs, CDK12 and CDK13 has further complicated matters.13

Notably, CDK7 also serves as a CAK and indirectly regulates the cell cycle by affecting the activity of cell cycle CDKs, which are its major targets, in addition to CDK9.14

**TARGETING TRANSCRIPTIONAL CDKs**

Normal gene transcription is often regulated by distal noncoding regulatory elements termed enhancers. Super-enhancers (SEs) are large clusters of enhancers that are densely occupied by master transcription factors, which drive transcription of genes involved in cell identity. SEs have also been found to be essential drivers of oncogenesis by facilitating high expression of oncogenes such as MYC. Cancer cells can become transcriptionally “addicted,” or reliant on altered, SE-driven

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**Table. Novel CDK Inhibitors in Clinical Development**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target(s)</th>
<th>Ongoing Trials (ClinicalTrials.gov identifier)</th>
</tr>
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</table>
| Alvocidib (TolerO Pharmaceuticals) | Primary: CDK9 Additional: CDKs 1, 2, and 4 | Phase II  
- chemotherapy following prior venetoclax with azacitidine or decitabine in R/R AML (NCT03964920)  
- + cytarabine and mitoxantrone in R/R AML with MCL1 dependence (NCT02520011)  
- + venetoclax in R/R AML (NCT03441555)  
- + venetoclax and daunorubicin in newly diagnosed AML (NCT03298894)  
- + decitabine in MDS (NCT03593915) |
| TP-1287 (TolerO Pharmaceuticals) | Primary: CDK9 Additional: CDKs 1 and 9 | Phase I  
- Monotherapy in advanced solid tumors (NCT03604783) |
| Dinaciclib (Merck) | Primary: CDKs 2 and 5 Additional: CDKs 1 and 9 | Phase I  
- + venetoclax in R/R AML (NCT03484520)  
- + veliparib in advanced solid tumors (NCT01434316)  
- + pembrolizumab in advanced breast cancer (NCT01676753) |
| CYC065 (Cyclacel Pharmaceuticals) | Primary: CDKs 2, 5, and 9 Additional: CDKs 3, 7, and 4 | Phase I  
- Monotherapy in advanced cancers (NCT02552953)  
- + venetoclax in R/R AML or MDS (NCT04017546)  
- + venetoclax in R/R CLL (NCT03795554) |
| Voruciclib (MEI Pharma) | Primary: CDK9 Additional: CDKs 6, 4, and 1 | Phase I  
- Monotherapy in R/R B-cell malignancies or AML (NCT03547115) |
| Zoliraciclib (TG02) (Adasta Pharmaceuticals) | Primary: CDK9 Additional: CDKs 2, 3, and 5 | Phase I or I/II  
- + temozolomide in adults with recurrent AA or glioblastoma (NCT02942264)  
- + temozolomide or RT in elderly patients with newly diagnosed AA or glioblastoma or as monotherapy in adults with relapsed disease (NCT03224104)  
- Monotherapy in recurrent high-grade glioma (NCT03904628) |
| SY-5609 (Syros Pharmaceuticals) | CDK7 | Phase I  
- Monotherapy in advanced solid tumors (NCT04247126) |
| CT001 (Carrick Therapeutics) | CDK7 | Phase I/II  
- + fulvestrant in advanced solid malignancies (NCT03638983) |
| SEL120 (Selvita) | CDK8 | Phase I  
- Monotherapy in AML or high-risk MDS (NCT04021368) |
| AZO4573 (AstraZeneca) | CDK9 | Phase I  
- Monotherapy in R/R hematologic malignancies (NCT03263637) |

AA indicates anaplastic astrocytoma; AML, acute myeloid leukemia; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; R/R, relapsed or refractory; RT, radiotherapy.
transcriptional programs that developed during tumorigenesis.\textsuperscript{15,16-18} This has opened new doors for the therapeutic targeting of transcriptional CDKs. Both CDK9 and CDK7 have been implicated in global transcriptional control by promoting the expression of genes regulated by SEs, including MTC.\textsuperscript{12,19} Thus, the requirement of some SEs for these CDKs has emerged as an important Achilles’ heel in cancer cells that could be targeted by CDK7 or CDK9 inhibition.\textsuperscript{20} This has also helped assuage concerns that transcriptional CDKs may make poor targets due to insufficient selectivity for cancer cells. Few of the first-generation, pan-CDK inhibitors are still in development because of their poor showing in clinical trials. Considering the evolving understanding of its transcription activity, alvocidib has been restyled as a “CD9 inhibitor.” It is being evaluated in early-phase trials that seek to exploit its association with SE-driven transcription factors, which are highly expressed in some hematologic malignancies. Notably, these transcription factors include the MCL1 protein, a negative regulator of apoptosis that is overexpressed in about half of cases of relapsed/refractory (R/R) acute myeloid leukemia (AML). Overexpressed MCL1 inhibits apoptosis and sustains the survival of leukemic blast cells, which drives relapse and resistance to therapy.\textsuperscript{22} Preclinical studies revealed increased sensitivity to alvocidib in patients whose tumors display MCL1 dependence.\textsuperscript{22} In the ongoing phase II Zella 201 study (NCT02520011), alvocidib is administered before cytarabine and mitoxantrone in patients with MCL1-dependent R/R AML. Among 25 patients enrolled in stage 1, 21 were evaluable for response; the overall rate of complete remission (CR) or CR with incomplete hematologic recovery (CRI) was 62%. The most common grade 3 or greater nonhematologic treatment-emergent adverse events (TEAEs) were tumor lysis syndrome (TLS), diarrhea, increased aspartate aminotransferase (AST), sepsis, and peripheral edema.\textsuperscript{22} Results of the ongoing phase I Zella 101 study (NCT03298984) of alvocidib followed by 7 + 3 induction chemotherapy in patients with newly diagnosed AML showed that alvocidib was well tolerated. Among 22 patients, the most common grade ≥3 nonhematologic TEAEs were diarrhea, hypophosphatemia, hypokalemia, and TLS.

Among 18 patients evaluable for response, 14 achieved CR or CRi.\textsuperscript{23} The clinical development of alvocidib is somewhat limited by its IV route of administration. For this reason, an oral prodrg of alvocidib, TP-1287, is also in development; a phase I study (NCT03604783) in patients with advanced solid tumors began in January 2019.\textsuperscript{24,25} CYC065 is another multitargeted CDK inhibitor that includes CDK9 among its targets, and ongoing phase I clinical trials in AML or myelodysplastic syndrome (MDS) and chronic lymphocytic leukemia are focusing on a combinatorial strategy with the BCL-2 inhibitor venetoclax (Venclexta). Upregulation of MCL1 has been shown to drive resistance to inhibitors of antiapoptotic proteins such as venetoclax, which could be overcome by indirectly targeting MCL1 through CDK9 inhibition.\textsuperscript{26} Preliminary data show that the combination of CYC065 and venetoclax was well tolerated, with no dose-limiting toxicities (DLTs) and no TLS. In the CYC065-03 study (NCT04017546), 3 of 9 patients with AML or MDS treated at doses ranging from 64 to 150 mg/m\textsuperscript{2} achieved a reduction in leukemia blast cells in their peripheral blood. In the CYC065-02 study (NCT03739554), 2 patients who had failed the Bruton tyrosine kinase inhibitor ibrutinib (Imbruvica), 1 of whom had also failed chimeric antigen receptor T-cell therapy, achieved shrinkage of enlarged lymph nodes by computed tomography scan at a dose of 64 mg/ m\textsuperscript{2} every 2 weeks; the latter patient was also negative for minimal residual disease.\textsuperscript{27} Zotiraciclib is the most potent CDK9 inhibitor developed to date, but it also strongly inhibits CDKs 1, 2, 3, and 5. The FDA recently granted the agent orphan drug designation for patients with glioma,\textsuperscript{28} a tumor type that often exhibits MYC messenger RNA expression.\textsuperscript{29} The designation was awarded based on an ongoing trial evaluating zotiraciclib in combination with temozolomide.\textsuperscript{30}

In intertumoral phase I trials, 40 patients were treated with zotiraciclib at a starting dose of 200 mg orally combined with temozolomide on either a dose-dense (125 mg/m\textsuperscript{2}/day, 7 days on, 7 days off) or metronomic (50 mg/m\textsuperscript{2}/day) dosing schedule. In all, 38 patients were evaluable, 18 in the dose-dense arm and 20 in the metronomic arm. In the dose-dense arm, DLTs included grade 3 diarrhea (200-mg dose) and grade 4 neutropenia, grade 3 elevated alanine aminotransferase (ALT), and grade 3 fatigue (250-mg dose). In the metronomic arm, DLTs included recurrent grade 3 neutropenia (200-mg dose); grade 3 elevated ALT, grade 3 fatigue, and grade 4 neutropenia (250-mg dose); and grade 4 elevated ALT, grade 4 elevated AST, and grade 4 febrile neutropenia (300-mg dose). The investigators reported that 4 patients completed 12 cycles of therapy with “prolonged disease control” but did not provide further details.\textsuperscript{4}

**SELECTIVE INHIBITORS**

Pharmaceutical companies are also eyeing more selective inhibitors of CDK9 and CDK7. AZD4573 is a highly selective IV CDK9 inhibitor with a half-maximal inhibitory concentration (IC\textsubscript{50}) of 14 nM and over 10-fold selectivity for CDK9 compared with 13 of the other 14 kinases tested. AZD4573 is being evaluated in a phase I clinical trial (NCT03263637) in R/R hematologic malignancies after preclinical studies demonstrated its ability to induce apoptosis in cancer cells across tumor cell lines and hematologic cancer models.\textsuperscript{30} SY-5609 is an oral, noncovalent inhibitor of CDK7 with an IC\textsubscript{50} of 60 nM. It is 49,000-, 16,000-, and 13,000-fold less selective for CDK2, 9, and 12, respectively.\textsuperscript{31} Syros Pharmaceuticals was originally developing an IV CDK inhibitor, SY-1365, but halted in 2019 to focus on SY-5609, which was more potent and selective and demonstrated greater antitumor activity in preclinical studies. The first patient in a phase I study in advanced solid tumors with RB pathway alterations was dosed in January 2020.\textsuperscript{32} CT7001 is another orally bioavailable CDK7 inhibitor, with an IC\textsubscript{50} of 40 nM and high selectivity over other kinases tested. Formerly known as ICE0942, CT7001 has demonstrated antitumor activity in preclinical models across a range of tumor types, including AML, small cell lung cancer, and hormone-sensitive triple-negative breast cancer. A phase I clinical trial was initiated at the end of 2017.\textsuperscript{33,34} Finally, SEL120 is a first-in-class selective inhibitor of CDK8. In preclinical AML xenograft models, it induced CR and demonstrated synergy with apoptosis-inducing drugs and chemotherapy.\textsuperscript{35} A phase I trial of SEL120 began in September 2019 (NCT04021368).\textsuperscript{36}
WHAT MATTERS MOST TO YOUR PATIENTS?

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A WAVE OF CHANGE HAS taken hold of the treatment landscape for triple-negative breast cancer (TNBC). Recent successes demonstrated in clinical trial data have led to the approval of new immunotherapy and targeted agents, thanks in part to the molecular classification of TNBC.

“Triple-negative breast cancer remains a very challenging area,” said Debu Tripathy, MD, who served as moderator for a recent OncLive Peer Exchange®. The expert panel focused on the development of immunotherapy and other notable successes based on recent presentations at the 2019 San Antonio Breast Cancer Symposium.

CHECKPOINT INHIBITORS
PD-L1 evaluation
PD-L1 status plays an important role in first-line treatment decisions for patients with TNBCs that are PD-L1-positive and it appears to be the best predictor of patient response to immune checkpoint inhibitors at this time. In determining whether a patient with TNBC would be an appropriate candidate for immunotherapeutic agents, the panelists agree that early PD-L1 testing is needed prior to initiating first-line treatment. However, “the determination of PD-L1 positivity has been reasonably controversial because there are a number of tests depending on the specific immune checkpoint inhibitor,” said Hope S. Rugo, MD, FASCO.

Currently, the SP142 (VENTANA PD-L1) immunohistochemical assay is the only approved PD-L1 companion diagnostic for TNBC, with ≥1% positivity needed for treatment with atezolizumab (Tecentriq) in combination with nab-paclitaxel (Abraxane).1-3

The panelists look forward to results from ongoing trials of PD-1/PD-L1 inhibitors that should provide more data on PD-L1 testing. “What we found was that PD-L1 still seemed to be the best determinant of response to atezolizumab… but I think we’re going to see a lot more data in the future,” said Rugo.

Once first-line treatment has begun, next-generation sequencing is increasingly important for management decisions. “I think there’s now evolving data for some of these, albeit rare, mutations, that could give us [a] potential target…. We should be doing next-generation sequencing in addition to PD-L1 testing,” said Ian E. Krop, MD, PhD. Panelists expressed interest in next-generation sequencing to help identify patients with TNBCs with AKT or NKR7 alterations that could be targeted with specific therapeutic agents.

IMpassion130 trial
The SP142 assay was validated in the phase III IMpassion130 trial (NCT02367781) that enrolled 902 patients with untreated metastatic TNBC and randomized patients to receive nab-paclitaxel with either atezolizumab or placebo. Patients continued treatment until disease progression or unacceptable toxicity. IMpassion130 trial end points were progression-free survival (PFS) and overall survival (OS) based on intention-to-treat (ITT) analyses.4
The median PFS was 7.2 months in the atezolizumab group compared with 5.5 months in the placebo group (HR for progression or death, 0.80; 95% CI, 0.69–0.92). For patients with PD-L1-positive tumors, median PFS was 7.5 months in the atezolizumab group compared with 5.0 months in the placebo group (HR, 0.62; 95% CI, 0.49–0.78).4 At the time of first interim analysis of the ITT population, the median OS was 21.3 months in the atezolizumab group compared with 17.6 months in the placebo group (HR for death, 0.84; 95% CI, 0.69–1.02; P = .08). For those patients with PD-L1-positive tumors, the median OS was 25.0 months in the atezolizumab group compared with 15.5 months in the placebo group (HR, 0.62; 95% CI, 0.45–0.86).4

Tripathy said that the wealth of PD-L1 biomarker data in IMpassion130 was “tremendously helpful.” The initial IMpassion130 trial results ultimately led to the approval of atezolizumab for use in combination with nab-paclitaxel for patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 ≥1%.2

However, the secondary interim analysis for the ITT population in IMpassion130 showed that median OS did not differ significantly between the atezolizumab and placebo groups (21.0 and 18.7 months, respectively; HR, 0.86; 95% CI, 0.72–1.02; P = .078) in the ITT population. Investigators noted that the exploratory comparison among patients with PD-L1-positive tumors showed a “clinically meaningful” OS benefit (25 vs 18 months; stratified HR, 0.71; 0.54–0.94).5 Serious adverse events (AEs) included neutropenia and peripheral neuropathy. In the IMpassion130 trial, there were 3 treatment-related deaths (2 in the treatment group and 1 in the placebo group).3 “We see some life-threatening toxicity and I say to people the key thing is any organ can be affected,” said Rugo. “If you see something funny and it doesn’t go away and you hadn’t seen it before, it’s immune-related, and so you should treat it.”

ANTIBODY-DRUG CONJUGATES

Another exciting area that the panelists discussed was the progress in treating metastatic TNBC with antibody-drug conjugates (ADCs). “We’re making big advances in various agents. But I think the ADCs are, to me, an exciting new area of investigation,” said Rugo. Targeted therapy also proved to be an area of great interest among the panelists. TROP-2 is overexpressed in 80% of patients with TNBC. For patients with metastatic disease “the median survivals are less than a year and the median PFS for most agents is in the range of 2 to 3 months,” said Adam M. Brufsky, MD, PhD.

Targeting TROP2 could afford better options for those patients with refractory metastatic TNBC, and efforts have begun with the agent sacituzumab govitecan.

SACITUZUMAB GOVITECAN

A total of 108 patients with metastatic TNBC who had received at least 2 previous anticanther therapies were enrolled into a phase I/II trial (NCT01631552) to receive sacituzumab govitecan until disease progression or unacceptable toxicity. The end points are objective response rate, duration of response, clinical benefit rate, PFS, and OS.6 The response rate was 34.3% and the median response duration was 9.1 months as assessed by independent central review. The clinical benefit rate was 45.4%. Median PFS and OS were 5.5 months and 13 months, respectively. With regard to AEs, 9.3% of patients experienced febrile neutropenia.6 “The overall survival clearly looked to be better than historical controls,” said Brufsky. Results from this trial led to the FDA accepting a new biologics license application for sacituzumab govitecan in December 2019 with an action date set for June 2, 2020. This follows an unsuccessful first outing for the agent, for which the FDA issued a complete response letter citing chemistry, manufacturing, and control matters as their primary concerns.24

The phase I/II results were impressive enough that there is speculation about whether, “the FDA [will] give the priority accelerated approval now or will they wait for the phase III. That’s the big question I think that everybody has in mind,” said Brufsky. The phase III ASCENT trial (NCT02574455) has finished accrual in the same patient population and disease state and will randomize 529 participants to either sacituzumab govitecan or physician’s choice chemotherapy.

“I think it would be great to see data from ASCENT [in 2020]. What’s interesting about this particular drug is that sacituzumab govitecan has an SN38, which is the active metabolite of irinotecan,” noted Rugo, who added that this reduces diarrhea as an AE but does not eliminate hair loss.

PARP INHIBITORS

PARP inhibitors are another therapeutic strategy for patients with TNBC who harbor either germline or somatic BRCA mutations. These patients account for approximately 20% to 25% of the TNBC population. Although the panelists note that progress in this area is not moving as quickly as it is in other areas, such as ovarian cancer, studies are under way to investigate the utility of PARP in this subset of patients.9

BROCADE3 Trial

In BROCADE3 (NCT02163694), 509 patients with BRCA-positive, previously treated metastatic TNBC were randomly assigned 2:1 to receive veliparib plus carboplatin/paclitaxel or placebo plus carboplatin/paclitaxel. Patients completing carboplatin/paclitaxel treatment without disease progression received veliparib or placebo maintenance.10 Median PFS was 19.3 months for the veliparib group versus 13.5 months in the placebo group (HR, 0.70; 95% CI, 0.54–0.90). At 3 years, the PFS was 26% for the veliparib group versus 11% for the placebo group.10 “There was a really big improvement in progression-free survival in favor of a maintenance strategy,” said Joyce A. O’Shaughnessy, MD.

“The curves actually separated when you started the maintenance,” added Brufsky. “They didn’t separate until you started the maintenance.”

DORA trial

One upcoming study that is generating interest among the panelists is the phase II DORA trial (NCT03167619). It is designed to explore the efficacy of olaparib with or without durvalumab (Imfinzi) as maintenance therapy for patients with metastatic TNBC who have demonstrated benefit with platinum-based chemotherapy. The primary end point will be PFS.11

CONTINUED ON PAGE 73
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Table. Select Phase II/III Neoadjuvant Immunotherapy Trials in TNBC12-14

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Therapy</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>KEYNOTE-522</td>
<td>Neoadjuvant chemotherapy with or without pembrolizumab (Keytruda)</td>
<td>pCR: 64.8% vs 51.2% (95% CI, 5.4%-21.8%; P = .00055)</td>
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<tr>
<td>NeoTRIPaPDL1 Michelangelo</td>
<td>Neoadjuvant chemotherapy with or without atezolizumab</td>
<td>pCR: 43.5% vs 40.8% (OR, 1.11; 95% CI, 0.69-1.79)</td>
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<tr>
<td>SAFIR02-IMMUNO</td>
<td>Durvalumab versus maintenance chemotherapy</td>
<td>Median OS: 21 vs 14 months (HR, 0.54; 95% CI, 0.30-0.97)</td>
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</table>

OS indicates overall survival; pCR, pathological complete response; TNBC, triple-negative breast cancer.

“I think the DORA trial, which is being conducted in triple-negative breast cancer, is really interesting,” said O’Shaughnessy. “Right now, we don’t have enough data to combine a PARP inhibitor with the checkpoint inhibitor in the first line. I think if a patient is germline-BRCA mutant and her cancer is PD-L1-positive, I will go where I know there’s a survival advantage in a phase III trial.”

NEOADJUVANT THERAPY

Panelists also focused on neoadjuvant therapy in TNBC. “There [have] been a lot of data now coming out from using immunotherapy in that setting with different checkpoint inhibitors,” Tripathy said (TABLE12-14).

KEYNOTE-522

The FDA granted pembrolizumab (Keytruda) plus neoadjuvant chemotherapy a breakthrough therapy designation for patients with early-stage TNBC after demonstrating manageable safety and antitumor activity in the KEYNOTE-173 and I-SPY2 trials. Investigators are further exploring the anti-PD-1 neoadjuvant chemotherapy combination in the KEYNOTE-522 (NCT03036448) trial.

The phase III trial randomized 1174 patients with early-stage TNBC 2:1 to receive neoadjuvant chemotherapy with or without pembrolizumab following definitive surgery. Patients continued treatment until recurrence or toxicity, and the primary end points were pathological complete response (pCR) and event-free survival (EFS).

Among patients whose cancers had lymph node involvement, the addition of pembrolizumab was associated with a 64.8% pCR rate compared with a 51.2% pCR rate in the placebo group.12

The KEYNOTE-522 findings showed “one of the highest pCR rates ever reported in a triple-negative population and a big population,” said Rugo. However, the panelists are looking forward to the full results of KEYNOTE-522 and other trials that “are powered by event-free survival, [which] should be our standard,” Rugo added. At the time of analysis, a favorable trend for EFS was observed in the pembrolizumab arm (HR, 0.63).12

SAFIR02 trial

The panelists also discussed SAFIR02-IMMUNO, a substudy of the SAFIR02_Breast trial (NCT02299999). In this phase II trial, patients with HER2-negative metastatic breast cancer who were eligible for or were currently being treated with first- or second-line chemotherapy underwent genomic evaluation. Those with preselected genomic alterations for which a targeted therapy was available were placed in a substudy of targeted therapy versus maintenance chemotherapy.

Patients with no targetable genetic alterations (n = 190) were randomized 2:1 to receive either durvalumab or maintenance chemotherapy. For 82 patients with TNBC, the median OS was 21 months with durvalumab compared with 14 months for chemotherapy (HR, 0.54; 95% CI, 0.30-0.97). Researchers also stratified results for patients with metastatic breast cancer (not only TNBC) whose tumors were PD-L1 positive (21%). Among the 44 patients with PD-L1-positive tumors, the median OS was 26 months for the durvalumab group compared with 12 months for the chemotherapy group (HR, 0.42; 95% CI, 0.17-1.05).14

The panelists were encouraged by both the TNBC findings and PD-L1 group findings, despite the latter not reaching statistical significance. Their discussion of why the trial failed to find a difference in the PD-L1 substudy focused on the small study size and the need for longer follow-up. “Maybe we need to give it in a different way or select the right group of patients. For example, if you took the responders to checkpoint inhibition, maybe it would have made a difference,” said Rugo.

LOOKING AHEAD

The recent increase in clinical trials and the options afforded to patients with TNBC point toward positive movement in the field. “We’re making big advances in various agents,” said Rugo. “The good news is that we have a lot of trials in this space. There’s been a lot of interest from the community in subscribing patients to these trials,” said Tripathy.

However, these advances also come with challenges. “I think this area is going to be really complicated by the fact that we’ve got a lot of trials and the events are going to be small. They’re not really, with the exception of some of the really large studies, powered to look at event-free survival,” added Tripathy.
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† The Primary Endpoint of Overall PFS was not met in this study.
1 van de Ven et al. / Clin Oncol 2016; 38: 1723–1731
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