Targeted Therapy Innovator Foresees New Paradigms in Breast Cancer

PEER EXCHANGE

CERVICAL CANCER Treatment Paradigm Is Bolstered With Newly Approved Treatments

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2021 SABCS

Elacestrant Shines in ESR1-Mutant Breast Cancer
Trastuzumab Deruxtecan Battles Second-line Standard for HER2+ Metastatic Disease
New Data Highlight Options for TNBC Subtypes

DRUG SPOTLIGHT

Ajai Chari, MD, Discusses Role of Subcutaneous Daratumumab in MULTIPLE MYELOMA

CLINICAL TRIAL IN FOCUS

CAR Macrophages Show Early Feasibility in HER2+ SOLID TUMORS

ROSWELL PARK COMPREHENSIVE CANCER CENTER

Robotic Navigational Bronchoscopy
Advances Diagnosis of Early-Stage LUNG CANCER

By Christopher S. Lathan, MD, MS, MPH

Debu Tripathy, MD
CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

Complex mechanisms of estrogen receptor (ER) signaling have been associated with tumor growth.\textsuperscript{1-3}
In ER+/HER2- mBC, the ER pathways are involved in tumor progression and treatment escape mechanisms that enable endocrine resistance.\textsuperscript{1,2,4,5}

To strengthen the fight against resistance, could advancements in ER antagonism and degradation help decrease the ER pathway’s downstream effects?

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Targeted Therapy Innovator Foresees New Paradigms in Breast Cancer

by CHRISTINA T. LOGUIDICE

As preparations for the 39th Annual Miami Breast Cancer Conference® commence, Debu Tripathy, MD, a cochair of the meeting, reviews the ever-shifting treatment landscape for patients with breast cancer and highlights how targeted therapies are the driving force behind many of the recent advances in the field.

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By Maurie Markman, MD

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Harnessing the Power of HER2

TARGETED APPROACHES TO CANCER treatment have blossomed as investigators seek to build on the foundational success of approved treatment. ERBB2, or HER2, is one such target that has been a prominent focus of investigation for patients with breast cancer.

For instance, the anticipated launches of 5 pipeline agents and the label expansions of marketed drugs, the HER2-positive breast cancer market is expected to experience low growth from 2020-2030, according to a report by data and analytics company GlobalData. The market is estimated to rise at a compound annual growth rate of 1.5%, from $10.4 billion to $12.1 billion, across the 8 major markets of the US, France, Germany, Italy, Spain, the UK, China, and Japan.1

Approved agents such as trastuzumab (Herceptin), pertuzumab (Perjeta), and ado-trastuzumab emtansine (T-DM1; Kadcyla) are the mainstays of the treatment paradigm for patients with breast cancer and newcomer fam-trastuzumab deruxtecan-nxki (Enhertu) are fast becoming welcome standards in later lines of treatment. In coverage of the 2021 San Antonio Breast Cancer Symposium, OncLive® highlighted the most recent data from several studies in HER2-expressing breast cancers, including the notable results from the subgroup analysis of trastuzumab deruxtecan vs T-DM1 in the DESTINY-Breast03 trial (NCT03529110).

As the integration of these new agents expand options for the population of patients with HER2-expressing tumors, investigators are also noticing trends in improved outcomes for those whose tumors have low levels or targetable expression. For example, in this month’s cover story, Debu Tripathy, MD, notes that the story for HER2 in breast cancer is adding a new chapter—one that includes patients with low or nonexpressing tumors as defined by immunohistochemistry: HER2-overexpressing (HER2 IHC3+ or HER2 IHC2+/ISH+); HER2 low-expressing (IHC1+ or IHC2+/ISH-); and HER2 nonexpressing (IHC0+). “[Trastuzumab deruxtecan] is probably one of the most potent drugs we have against HER2 cancers,” Tripathy said. “It turns out that it may also work in HER2-low cancer.”

Elsewhere, investigators are seeking to further tap the potential of HER2 in solid tumors with the development of the chimeric antigen receptor (CAR) macrophage, CT-0508. This issue’s Clinical Trial in Focus section highlights early safety and feasibility data of the novel treatment from the first-in-human, multicenter, phase 1 study (NCT04660929) of adenovirally transduced anti-HER2 CAR macrophage.

HER2 will be top of mind for Tripathy in March, when he will serve as a cochair of the 39th Annual Miami Breast Cancer Conference® hosted by Physicians’ Education Resource® (PER®), LLC, as a live and virtual meeting in Miami Beach, Florida. Leading breast cancer investigators will host a broad range of sessions, tumor board panels, multidisciplinary meet-the-expert sessions, poster talks, and debates, some of which will distill the latest data concerning HER2 agents into clinical practice.

REFERENCE

As always thanks for reading,
Mike Hennessy Jr
President and CEO
MJH Life Sciences™
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

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

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

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

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

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

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

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

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

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

ADVERSE REACTIONS
The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

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

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

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

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

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

Please see Brief Summary on the following pages.

Infections:
Fungal and non-fungal infections (including viral, bacterial, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater viremia was observed in 0.2% of patients. Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, history of acute infections, and a previous history of cardiac arrhythmias (see Adverse Reactions).

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

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Monitor complete blood counts monthly.

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Monitor complete blood counts monthly.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia (5% in the IMBRUVICA arm vs 6% in the ofatumumab arm) occurred in patients.

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

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

Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

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

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

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 (17)</td>
<td>2 (2)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (16)</td>
<td>0 (0)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12 (11)</td>
<td>0 (0)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>32 (29)</td>
<td>0 (0)</td>
<td>25 (22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53 (49)</td>
<td>4 (4)</td>
<td>27 (24)</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53 (49)</td>
<td>30 (27)</td>
<td>70 (61)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43 (39)</td>
<td>7 (6)</td>
<td>69 (62)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26 (23)</td>
<td>0 (0)</td>
<td>51 (45)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13 (12)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>12 (11)</td>
<td>5 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (11)</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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

† Includes one event with a fatal outcome.

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

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades</td>
<td>Grade 3 or Higher (%)</td>
</tr>
</tbody>
</table>
| Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less).

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53 (49)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43 (39)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26 (23)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria

Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (N=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of venous, arterial,ular or pulmonary embolism, atherosclerotic event, artery thrombosis, venous thrombosis, peripheral artery disease, cerebrovascular event, venous thromboembolism, peripheral artery disease, cerebrovascular event, venous thromboembolism, and arterial thrombosis, was 4.6% versus 6.0% and 5.9% versus 7.6% in IMBRUVICA-treated patients compared to patients in the control arm, respectively.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors of CYP3A.

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

**DRUG INTERACTIONS**

**Effect of CYP3A Inhibitors on Ibrutinib:** the coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib plasma concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate CYP3A inhibitors of CYP3A.

**Use in Specific Populations**

**Pregnancy:** Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2.20 times the clinical doses of 600-900 mg daily producing embryolethal findings (see Data). Advise pregnant women of the potential risk to a fetus.

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

**Additional Important Adverse Reactions: Cardiovascular Events:** Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (N=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of venous, arterial, or pulmonary embolism, atherosclerotic event, artery thrombosis, venous thrombosis, peripheral artery disease, cerebrovascular event, venous thromboembolism, peripheral artery disease, cerebrovascular event, venous thromboembolism, and arterial thrombosis, was 4.6% versus 6.0% and 5.9% versus 7.6% in IMBRUVICA-treated patients compared to patients in the control arm, respectively.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors of CYP3A.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate CYP3A inhibitors of CYP3A.

**Use in Specific Populations**

**Pregnancy:** Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2.20 times the clinical doses of 600-900 mg daily producing embryolethal findings (see Data). Advise pregnant women of the potential risk to a fetus.
Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MCL) and 28 times the exposure in patients with CLL/SLL or Waldenström’s Macroglobulinemia (WM) administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibritinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.8 times the exposure (AUC) in patients with MCL and 1.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose.

Females and Males of Reproductive Potential: Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating IMBRUVICA.

Contraception: Females: IMBRUVICA can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose.

Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

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

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

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Active ingredient made in China.

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

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PRC-07287
Although OS should certainly be a secondary end point of a randomized trial examining therapeutic efficacy in individuals with advanced and metastatic cancers, it should not be the mandated primary study end point, where reasonable therapeutic options exist for patients who complete trial-based therapies.”
Depending on the status of the investigative drug in question, a study may permit crossover to the experimental arm of a trial (if the patient desires such therapy) or, if the agent is commercially available, the patient’s oncologist may simply elect to employ the drug in future care.

It is essential to note that what is described above has nothing to do with the clinical utility of the investigative arm in question but rather the natural history of disease and its treatment after a research subject receiving protocol-defined therapy has re-entered the domain of standard of care or innovative nonresearch clinical management options.

THE PROOF IS IN THE DATA
The effect of the availability or lack of availability of possibly beneficial next-line therapy options on the survival outcome of patients participating in randomized trials was highlighted in a report of the relationship between PFS and OS in the initial evaluation of the first generation of truly useful antineoplastic agents for metastatic melanoma.

In an analysis of 9 randomized trials that employed dacarbazine (an almost completely inactive chemotherapeutic agent given for several decades in the treatment of this condition) as a control arm that permitted no crossover to the investigative drug, a very close relationship (correlation coefficient 0.96) between the study defined PFS, and the subsequently documented OS was documented.2 As noted above, this outcome resulted from the lack of known clinically beneficial next-line therapeutic options in this era for the management of metastatic melanoma.

However, in a report published 6 years later, investigators examined trial outcomes in which the experimental arm was checkpoint inhibitor therapy and the control arm was dacarbazine, but there was no difference in OS where subsequent therapy with the immunotherapy was permitted, despite a striking difference in PFS between the study arms.1 Does this mean the checkpoint inhibitor was not effective in the illness?

Absolutely not. In fact, patients randomized to the experimental regimen and the ineffective chemotherapy (dacarbazine) benefitted from their series of treatments. It would be a travesty to conclude otherwise, and yet one must note that the results of this study revealed no improvement in OS between the participants randomized to the investigative and control arms.

Multiple examples can be provided of the inability of a favorable effect of PFS to be converted into a statistically significant improvement in OS, but this should not be necessary to understand the point of this commentary. Advanced and metastatic cancers are increasingly being converted into serious, life threatening, and likely (although certainly no longer universally) fatal chronic diseases, where extended survivals are often measured in many years because of the availability of increasingly effective, often multimodality, approaches. As a result, it will become much more difficult to define the effect on OS of a single trial-based management strategy.

Although OS should certainly be a secondary end point of a randomized trial examining therapeutic efficacy in individuals with advanced and metastatic cancers, it should not be the mandated primary study end point, where reasonable therapeutic options after a patient completes trial-based therapy currently exist.

REFERENCES
Adjuvant Pembrolizumab Gains Approval for Melanoma
The FDA has approved pembrolizumab (Keytruda) for the adjuvant treatment of adult and pediatric patients aged 12 years and older with stage IIB or IIC melanoma following complete resection (CR).

The indication was supported by efficacy data from the first interim analysis of the phase 3 KEYNOTE-716 trial (NCT03553836), which showed pembrolizumab elicited a statistically significant improvement in recurrence-free survival (RFS). Specifically, pembrolizumab reduced the risk of disease recurrence or death by 35% (HR, 0.65; 95% CI, 0.46-0.92; \( P = .0132 \)) vs placebo. The median RFS was not reached in the investigative and control arms. After a median follow-up of 14.4 months, 54 of the 487 patients (11%) who received the immunotherapy experienced a recurrence or died vs 82 of the 489 patients (17%) who received placebo.

The regulatory agency also expanded the approval of the agent for the adjuvant use in patients with stage III melanoma following CR to include pediatric patients aged 12 years and older.

Efficacy in pediatric patients 12 years and older with stage IIB, IIC, or III melanoma is based on extrapolation of efficacy findings from adults, given similar biology, pharmacology of drug effect, and exposure-response for efficacy and safety.

FoundationOne CDx Gets Greenlight for Melanoma
The FDA has approved FoundationOne CDx for use as a companion diagnostic for 2 groups of current and future regulatory-approved treatments in melanoma, including single-agent BRAF inhibitors targeting BRAF V600E mutations and BRAF/MEK combination regimens targeting BRAF V600E or V600K mutations.

Currently, the companion diagnostic will be used for selecting appropriate patients for the combination of encorafenib (Brafvot) plus binimetinib (Mekint); and dabrafenib (Tafinlar) plus trametinib (Mekinist) in patients with melanoma.

Forthcoming, the assay will automatically become a companion diagnostic for BRAF inhibitors that are approved by the regulatory agency if they fall under these groups.

The assay is approved for use as a companion diagnostic across several indications, including non–small cell lung cancer, breast cancer, ovarian cancer, and prostate cancer. In melanoma, the test is used to select patients who harbor BRAF V600E mutations and may benefit from single-agent dabrafenib or vemurafenib (Zelboraf), or those with BRAF V600E or V600K mutations who should receive trametinib or cobimetinib (Cotellic) in combination with vemurafenib.

Abatacept Acquires Authorization for Acute GVHD
The FDA has approved abatacept (Orencia) for the prophylaxis of acute graft-vs-host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adult and pediatric patients aged 2 years and older undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor. This is the first agent to receive regulatory approval for prevention of this condition, and the decision was based on real-world evidence as a component detailing its clinical efficacy.

At 6 months following transplantation, results from the GVHD-1 trial (NCT01743131) showed that abatacept did not significantly improve aGVHD-survival vs placebo at 87% (n = 64/73) vs 75% (n = 52/69), respectively (HR, 0.55; 95% CI, 0.26-1.18). However, it did improve the overall survival (OS) rate at 97% vs 84%, respectively (HR, 0.33; 95% CI, 0.12-0.93). The moderate to severe aGVHD-survival rate was 50% in the investigative arm vs 32% in the control arm (HR, 0.54; 95% CI, 0.35-0.83).

Additionally, investigators used evidence from the GVHD-2 study—which leveraged real-world findings from the Center for International Blood and Marrow Transplant Research—showed that at 6 months posttransplantation, the OS rate was 98% (n = 53/54) for patients who received abatacept in combination with a calcineurin inhibitor and methotrexate compared with 75% (n = 122/162) for patients who received a calcineurin inhibitor and methotrexate alone.

Imaging Agents TLX591-CDx, Pafolacianine Receive Approvals for Prostate, Ovarian Cancers
The FDA has approved TLX591-CDx (Illucix) as a radioactive diagnostic agent for PET of prostate-specific membrane antigen positive lesions in patients with prostate cancer who have suspected metastasis who are candidates for initial definitive therapy, and in those with suspected recurrence based on elevated serum prostate-specific antigen level. The FDA also approved pafolacianine (Cytalux) as an optical imaging agent as an adjunct for interoperative identification of malignant lesions in adult patients with ovarian cancer.

Data from 2 prospective, open-label trials—the PSMA-PreRP (NCT02919111) and PSMA BCR (NCT02918357) studies—supported the approval of TLX591-CDx. Findings from the PSMA-PreRP trial showed that, for those with PET-positive disease, the positive predictive value was 61% (95% CI, 41%-81%). The PSMA BCR study demonstrated that 91% (n = 192/210) of patients were found to be true positive in at least 1 region against the composite reference standard (95% CI, 88%-95%).

Efficacy for pafolacianine was evaluated in a single-arm, open-label study (NCT03180307), which proved that 26.9% (n = 36/134) of patients had PET-positive disease, the positive predictive value was 61% (95% CI, 41%-81%), and the negative predictive value was 94% (95% CI, 84%-99%).


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**Drug Spotlight | DARATUMUMAB AND HYALURONIDASE-FIHJ (DARZALEX FASPRO)**

**Subcutaneous Daratumumab Plus Kd Is a “Gamechanger” for Patients With Multiple Myeloma**

**by JACKIE COLLINS**

**BASID ON DATA FROM** the phase 2 PLEIADES trial (NCT03412565), the FDA has approved daratumumab and hyaluronidase-fihj (Darzalex Faspro) plus carfilzomib (Kyprolis) and dexamethasone (Kd) for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.1

Investigators reported that response rates with the subcutaneous formulation of daratumumab plus Kd in PLEIADES were similar to those with intravenous (IV) daratumumab (Darzalex) plus Kd observed in the phase 3 CANDOR trial (NCT03158688). Distinctively, in a single-arm cohort of 66 patients in the PLEIADES study, the novel regimen elicited an 84.8% (95% CI, 73.9%-92.5%) overall response rate and a 77.3% very good partial response or better at a median follow-up of 9.2 months. The median duration of response with the regimen had not yet been reached. An estimated 85.2% of patients (95% CI, 72.5%-92.3%) continued to respond to treatment for at least 6 months and an estimated 82.5% of patients (95% CI, 68.9%-90.6%) maintained a response for at least 9 months.2

In an interview with OncologyLive®, Ajai Chari, MD, reviewed the takeaways from the PLEIADES trial and its comparability with the CANDOR trial, and how a subcutaneous formulation of a daratumumab combination became a pivotal player in the treatment enhancement for this patient population. Chari is a professor of medicine at Icahn School of Medicine at Mount Sinai in New York, New York.

**a** Describe the rationale for PLEIADES and how the importance of identifying an efficacious subcutaneous formulation of a daratumumab combination played into this.

One of the most important additions to our arsenal for myeloma [was daratumumab, which] was initially approved in 2015 as a monotherapy but quickly moved throughout the myeloma continuum in combination with many other agents: [IV] daratumumab was approved with bortezomib (Velcade), lenalidomide (Revlimid), and pomalidomide (Pomalyst). Subsequently, the arrival of subcutaneous daratumumab is a game changer because [it has] comparable efficacy with a much shorter infusion time. Median infusion time can be 6 to 8 hours, and [the subcutaneous treatment] is 3 to 5 minutes, which is particularly important in the era of COVID-19 to minimize exposure for both patients and hospital workers.

It’s much more convenient, [shows] comparable efficacy, and is safer—free of high-grade infusion reactions. [Subcutaneous daratumumab] has been approved in combination with bortezomib, lenalidomide, and pomalidomide. We didn’t have the combination of [subcutaneous daratumumab plus] carfilzomib approved and that’s what is important about this update.

**b** What were the key takeaways from the analysis of PLEIADES?

What [investigators of the] PLEIADES study did was look at various daratumumab combinations in the subcutaneous formulation. Key takeaways were that subcutaneous daratumumab has comparable efficacy and pharmacokinetics to what you would expect based on monotherapy and IV combinations of the respective agents.

In 2022 and beyond, I don’t see the role for IV daratumumab anymore. When you have such an efficacious, convenient, and well-tolerated agent—first and foremost for the patients but also for our nurses and pharmacists—it makes sense to be using subcutaneous daratumumab.

**c** How do the efficacy data with subcutaneous daratumumab plus Kd in PLEIADES build on what was observed with IV daratumumab plus Kd in CANDOR?

The PLEIADES study follow-up is much shorter [with] a medium follow-up of only 9.2 months, and the response rate was 85%. In the [CANDOR] study, [for which we just got an update [published in Lancet Oncology]], we have much more mature follow-up of approximately 28 months. The [median] PFS was 28.6 months in the triplet arm [daratumumab plus Kd] vs 15.2 months in the control arm.

What’s important and striking about this regimen is in lenalidomide-refractory patients, the PFS was no different. A majority of patients, especially in the United States, are getting lenalidomide in initial therapy and are also getting lenalidomide maintenance. By relapse, these patients are refractory to lenalidomide, and almost all other regimens to date have shown worse outcomes [for this population]. The fact that CANDOR had more mature data that show a PFS [benefit] even for [patients who are] lenalidomide refractory was so encouraging. That’s what is a gamechanger for this regimen.

Now that we have the subcutaneous formulation approved, it’s even better because [we can] deliver carfilzomib and Kd with subcutaneous daratumumab and get these impressive PFS results.

**What adverse effects should clinicians be aware of when prescribing subcutaneous daratumumab plus Kd?**

The adverse [effect] profile is [consistent with] what you see with each individual monotherapy. Subcutaneous daratumumab showed relatively low rates of infusion-related reactions—less than 10%. With carfilzomib, you usually have to watch out for dose-related hypertension, dyspnea, and thrombocytopenia. And then, of course, for Kd we are familiar with [the safety profile]. There is nothing new from this combination to worry about.

**For both patients and clinicians, what are the advantages and disadvantages of dosing or using IV to administer daratumumab?**

It’s a drug [that is convenient for] patients because efficacy is comparable, and pharmacokinetics favors subcutaneous daratumumab because when you go to monthly daratumumab you have a slightly higher trough level of the drug. The safety profile is better because of lower rates of infusion-related reactions.

Convenience is hard to beat; it’s 3 to 5 minutes and also a lot less volume. You’re not giving a large volume of fluid to patients, which, especially with carfilzomib, is important because we know that carfilzomib increases hypertension. We certainly don’t want to be adding fluids to these patients continuously. To be able to give the drug subcutaneously is much better; it makes better sense.

**What does the future hold for patients beyond subcutaneous daratumumab plus Kd?**

In the transplant-eligible population, we’re going to have a sizable number of [patients who are] daratumumab sensitive or daratumumab naive. [However,] in the transplant-eligible population, because of the increasing use of daratumumab up front, we may need alternative strategies. We’re excited about T-cell redirection therapies for TD30-refractory patients, [who] typically would not be eligible for CANDOR and PLEIADES.

**REFERENCES**

**Baseline Patient Characteristics**

**Median age (years, range)**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>N = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>42-84</td>
<td>61</td>
</tr>
</tbody>
</table>

**Stage of multiple myeloma at baseline**

- 14% Stage I
- 68% Stage II
- 18% Stage III

**Types of prior therapies**

- 79% ASCT
- 91% PI
- 100% Lenalidomide

**Refractory to lenalidomide at baseline**

- 62% Yes
- 38% No

**Commonly Reported Adverse Effects in the Pleiades Trial**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>All grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>52%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39%</td>
<td>2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>33%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Pivotal Clinical Trial**

PLEIAD (NCT03412565) was a multicohort, open-label trial evaluating the subcutaneous formulation of daratumumab combination therapy in patients with relapsed or refractory multiple myeloma who had received at least 1 prior line of therapy.

**Efficacy in the Pleiades Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Daratumumab and hyaluronidase plus carfilzomib and dexamethasone (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>84.8% (73.9%-92.5%)</td>
</tr>
<tr>
<td>sCR</td>
<td>16.7%</td>
</tr>
<tr>
<td>CR</td>
<td>21.2%</td>
</tr>
<tr>
<td>VGPR</td>
<td>39.4%</td>
</tr>
<tr>
<td>PR</td>
<td>7.6%</td>
</tr>
<tr>
<td>Ongoing response ≥ 6 months (95% CI)</td>
<td>85.2% (72.5%-92.3%)</td>
</tr>
<tr>
<td>Ongoing response ≥ 9 months (95% CI)</td>
<td>82.5% (68.9%-90.6%)</td>
</tr>
</tbody>
</table>

CR: complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

**Warnings and Precautions**

- Hypersensitivity and other administration reactions
- Cardiac toxicity in patients with light-chain amyloidosis
- Neutropenia
- Thrombocytopenia
- Embryo-fetal toxicity
- Interference with serological testing
- Interference with determination of complete response

**References**

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients¹-³

Consistent results with or without prior adjuvant chemotherapy²⁺

- Patients in the ADAURA trial are treated with ORAL TAGRISSO FOR 3 YEARS or until disease recurrence or unacceptable toxicity³

**INDICATION**

- TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

**SELECT SAFETY INFORMATION**

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

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¹Median DFS was not reached for TAGRISSO (95% CI: 58.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.¹
²Control arm=placebo.
³Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).²
⁴CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

**REFERENCE**

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TEST every surgical specimen for EGFR mutations
CHOOSE adjuvant TAGRISSO for every eligible patient

ADAURA study design: Phase III, double-blind, randomized, placebo-controlled trial in 682 patients with completely resected stage IB, II, and IIIA NSCLC with or without adjuvant chemotherapy. NSCLC patients had centrally confirmed EGFR mutations (exon 19 deletion or L858R mutation). Patients were stratified by stage (IB vs II vs IIIA), EGFR mutation (exon 19 deletion or L858R), and race (Asian vs non-Asian). Patients were randomized to either TAGRISSO (n=339; 80 mg orally, once daily) or placebo (n=343). The maximum interval between surgery and randomization was 26 weeks with adjuvant chemotherapy and 10 weeks without adjuvant chemotherapy. The primary endpoint of the study was DFS as determined by investigator assessment in stage II/IIIA patients. The secondary endpoints were DFS in the overall population (stage IB/II/IIIA), DFS rate at 2, 3, 4, and 5 years, overall survival (stage II/IIIA and overall population), safety, and health-related QoL. The planned treatment duration was 5 years or until disease recurrence/unacceptable toxicity.1,2,4

SELECT SAFETY INFORMATION

- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.6% were found to have a QTc >500 msec, and 3.1% of patients had an increase from baseline QTc >600 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with a prolonged QTc interval or those with concomitant QTc prolonging medications, congenital QTc prolongation, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.

- Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline LVEF and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO.

- Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

- Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

- Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. If cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.

- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

- Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough.

TAGRISSO™ (osimertinib) tablets, for oral use
Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.
INDICATIONS AND USAGE
Administration (2.4) and Adverse Reactions (2.4) in the full Prescribing Information.

QTc Interval Prolongation
Recent increases in QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 6% were found to have a QTc > 500 msec, and 3% of patients had an increase from baseline QTc > 500 msec. (See Clinical Pharmacology (12.2) in the full Prescribing Information). No QT-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, congenital heart disease, QT prolongation anomalies, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia (See Dosage and Administration (2.4) in the full Prescribing Information).

Cardiomyopathy
Across clinical trials, cardiomyopathy defined as cardiac failure, chronic cardiac failure, pericardial failure, peripheral edema, or decreased ejection fraction occurred in 3% of the 1479 TAGRISSO-treated patients: 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10 percentage points from baseline to ≤50% LVEF occurred in 0.3% of patients who had baseline and at least one follow-up EUGA. In the ADAURA study, 1.5% (5/205) of patients treated with TAGRISSO experienced LVEF decreases greater than or equal to 10 percentage points from baseline [see Warnings and Precautions (5.4) in the full Prescribing Information].

Cardiovascular
Cardiovascular disease (2.4) and Adverse Reactions (2.4) in the full Prescribing Information.

Gastrointestinal Disorders
Anemia‡ 30 0 12 0.3
Decreased appetite 13 0.6 3.8 0
Diabetes mellitus† 27 2.3 6.6 0.3
Glucose disorders† 35 2.9 9.7 0.3
Hypercarnitemia 18 0.3 0.3 0
Hypertension 45 3.9 9.7 0.3
Mucositis and Connective Tissue Disorders
Abdominal Pain** 12 0.3 7 0
Anemia 30 0 12 0.3
Anorexia 25 2.1 6.6 0.3
Aphthous stomatitis 20 0.6 0.3 0
Alopecia 29 1 13 0.5
Alopecia areata 15 0.5 0.3 0
Alopecia totalis 5 0.1 0.1 0
Alopecia universalis 5 0.1 0.1 0
Aphthous ulceration 15 0.6 0.6 0
Atrioventricular block 15 0.6 0.6 0
Atrioventricular node blockade 20 0.6 0.6 0
Bradycardia 15 0.6 0.6 0
Bronchitis 10 0.4 1 0
Cough 10 0.4 1 0
Cutaneous vasculitis including leukocytoclastic vasculitis, cutaneous urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

Malignant Neoplasms and Neoplasia
Metastatic disease (2.4) and Adverse Reactions (2.4) in the full Prescribing Information.

Skin Disorders
Cutaneous vasculitis
Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, cutaneous urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

Endothelial Toxicity
Based on data from animal studies and its mechanism of action, TAGRISSO can cause fatal form of pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH), which cause post-implantation fetal loss when administered during early development at a dose exposure to lung that approximates or exceeds the human systemic exposure. Pregnant females were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss of plasma exposures of approximately 0.5 times those observed at the recommended clinical dose. Therefore, TAGRISSO therapy should be avoided in pregnant women with the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and women who are of reproductive potential to use effective contraception for 4 months after the final dose (see Warnings and Precautions (5.4) in the full Prescribing Information).

Cardiovascular Disorders
Cardiovascular disease (2.4) and Adverse Reactions (2.4) in the full Prescribing Information.

Infections and Infestations
Nasopharyngitis 14 0 10 0
Upper respiratory tract infection 13 0.6 10 0
Urinary tract infection§ 15 0.7 7 0

Metabolism and Nutritional Disorders
Dehydration† 13 0.8 3.8 0
Hyperglycemia 25 2.3 30 0.9
Hyponatremia 20 1.8 16 1.5
Hyperuricemia 18 0.3 0.3 0
Hypothyroidism 12 0.5 1 0
Hypophosphatemia†† 18 0.3 0.3 0
Hypothyroidism 20 1.8 16 1.5
Hypokalemia 24 2.0 30 0.9
Hypoglycemia 25 2.3 30 0.9
Hypophosphatemia†† 18 0.3 0.3 0
Hypothyroidism 20 1.8 16 1.5
Hypoglycemia 25 2.3 30 0.9
Hypophosphatemia†† 18 0.3 0.3 0

QTc interval > 470 msec was the primary cardiovascular safety criterion used in the ADAURA protocol for selecting patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC who had complete tumor resection, with or without practicing chemotherapy. At the time of analysis median values of QTc for TAGRISSO was 22.3 months.

Serious adverse reactions were reported in 4% of patients treated with TAGRISSO. The most frequent serious adverse reaction (≥7% was pneumonitis (3.2%), pleuropneumonia (2.1%), and pulmonary embolism (0.8%). Dose reductions occurred in 2% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were pneumonitis (2.9%), pleuropneumonia (2.1%), and pulmonary embolism (0.8%).

Cardiomyopathy
Cardiomyopathy (2.4) and Adverse Reactions (2.4) in the full Prescribing Information.

Statistical analysis of exposure and response data from three clinical trials (F1 Flaura [1:1 randomised, 2:1 active vs placebo]), AURA2 (2:1 randomised, 2:1 active vs placebo), and AURA3 (1:1 randomised, 1:1 active vs placebo) indicated that the most common laboratory abnormality occurring in >5% of patients receiving TAGRISSO was hyponatremia (15%). The next most common laboratory abnormality occurring in >5% of patients receiving TAGRISSO was anemia (13%).

Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADAURA

† QTc interval > 470 msec was the primary cardiovascular safety criterion used in the ADAURA protocol for selecting patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC who had complete tumor resection, with or without practicing chemotherapy. At the time of analysis median values of QTc for TAGRISSO was 22.3 months.

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† Cardiomyopathy (2.4) and Adverse Reactions (2.4) in the full Prescribing Information.
Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 28% when co-administering with a strong CYP3A4 inducer. No serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (LD pneumomediastinum).

Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (18%), neutropenia (1%), and diarrhea (1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO is hepatic impairment (13%).

Tables 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA.

### Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3/4 (%)</th>
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</tr>
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<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>8</td>
<td>38</td>
<td>4.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32</td>
<td>3.3</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>37</td>
<td>0</td>
<td>31</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>30</td>
<td>0.7</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Creatine</td>
<td>25</td>
<td>1.2</td>
<td>8</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased ALAT</td>
<td>22</td>
<td>1.5</td>
<td>43</td>
<td>3.1</td>
</tr>
<tr>
<td>Increased AST</td>
<td>21</td>
<td>0.7</td>
<td>52</td>
<td>1.2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>16</td>
<td>0.4</td>
<td>22</td>
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</tr>
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</table>

### Table 5. Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients in FLAURA

<table>
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<tr>
<th>Laboratory Abnormality</th>
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<td>Hyperkalemia</td>
<td>16</td>
<td>0.4</td>
<td>22</td>
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</tr>
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</table>

**Effects of Osimertinib on Other Drugs**

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP or P-gp) or substrate can increase the exposure of the substrate compared to administering TAGRISSO alone [see Clinical Pharmacology (12.3) in the full Prescribing Information]. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the substrates unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

**US IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on data from animal studies and its mechanism of action [see Clinical Pharmacology (12.2) in the full Prescribing Information], TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on osimertinib in pregnant women. Administration of osimertinib to pregnant rats was associated with embryopathy and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose [see Data]. Advice pregnant women of the potential risk to their fetus.

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

**Animal Data**

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 3-20) to a pregnant plasma exposure of approximately 1.5 times the osimertinib clinical exposure, the most notable finding was increased post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the end of organogenesis (gestation days 3 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an incremental increase in the rate of fetal malformations and variations was observed at plasma exposures relative to human clinical exposures. When administered to pregnant rats at doses of 10 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth increased in magnitude between lactation days 4 and 6.

**Lactation**

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects on the breastfed infant are not known. Advise breastfed women to discontinue breastfeeding until further information becomes available.

**Contraception**

Females

Advice females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose [see Use in Specific Populations (8.7) in the full Prescribing Information].

Males

Advice male patients with female partners of reproductive potential to use effective contraception during treatment for and for 4 months following the last dose of TAGRISSO [see Nonclinical Toxicology (15.1) in the full Prescribing Information].

**Infertility**

Based on animal studies, TAGRISSO may impair fertility in males and females of reproductive potential. It is not known whether the effects on male fertility are reversible [see Nonclinical Toxicology (15.1) in the full Prescribing Information].

**Pediatric Use**

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

**Geriatric Use**

**Drug Interactions**

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increased TAGRISSO dose when co-administering with a strong CYP3A4 inducer is not recommended because it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue: Steven-Johnson syndrome, erythema multiforme, Stomatitis

**Nonclinical Toxicology**

Based on data from animal studies and its mechanism of action [see Nonclinical Toxicology (13.1) in the full Prescribing Information], TAGRISSO is a P-gp substrate. Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone [see Clinical Pharmacology (12.3) in the full Prescribing Information]. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A inducer if concurrent use is needed for the patient. Increase the TAGRISSO dosage when co-administering with strong CYP3A4 inducers to achieve a clinically effective exposure of TAGRISSO.

**Clinically Relevant Laboratory Abnormalities in AURAs**

Clinical relevant laboratory abnormalities in AURAs occurred in ≥20% of patients receiving TAGRISSO, and included increased blood creatinine (9%).

**Laboratory Abnormalities**

Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 28% when co-administering with a strong CYP3A4 inducer. No serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (LD pneumomediastinum).

Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (18%), neutropenia (1%), and diarrhea (1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO is hepatic impairment (13%).

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**Postmarketing Experience**

In its approved labeling, when co-administered with TAGRISSO.

BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the substrates unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

**Drug Interactions**

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone [see Clinical Pharmacology (12.3) in the full Prescribing Information]. Decreased osimertinib exposure may lead to reduced efficacy.
NEARLY 35 YEARS AGO, when Debu Tripathy, MD, was a fellow at the University of California, San Francisco, he became involved with a translational project that would help shape his career and cement his passion for research. “I joined a project to turn off this new oncogene that had been discovered recently called HER2. My job in the lab was to turn it off using antisense DNA. As a control, I needed to have a good antibody that worked against HER2-positive breast cancer cells. Genentech was right down the road from us. I knew some of the [investigators] there, and they gave me this antibody that is now Herceptin [trastuzumab],” he recalled.

Tripathy continued to study trastuzumab from the initial early phases through the late-stage trials that ultimately led to the monoclonal antibody’s approval. It proved to be a golden opportunity. “I was a fellow going on to become junior faculty when I got to be 1 of the 3 physicians who presented the data to the FDA when Herceptin got approved in 1998. That was a really special accomplishment for me,” he said.

Today, Tripathy is a professor and chair of the Department of Breast Medical Oncology, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston. His role in the development of trastuzumab, which introduced a new era in the treatment of HER2-positive breast cancer, marks an early milestone in a career packed with diverse research projects.

Over the years, Tripathy has continued to pursue novel drug targets and treatments along with developing models of patient-centered care and assessing complementary therapies.

He also has become a leader in the breast oncology community. In March 2022, Tripathy will again serve as a cochair of the 39th Annual Miami Breast Cancer Conference®, a role he has filled since 2012. Physicians’ Education Resource® (PER®), LLC, is hosting the conference Thursday, March 3, through Sunday, March 6, as a live and virtual meeting in Miami Beach, Florida. The hybrid conference will feature a broad range of sessions, tumor board panels, multidisciplinary meet-the-expert sessions, poster talks, and debates.

Tripathy finds the impact that research can have on his patients’ lives especially meaningful. He recounted the story of a patient he saw early in his career when trastuzumab was still in its infancy. The patient had advanced metastatic breast cancer with significant liver involvement, and she barely met the inclusion criteria for the trastuzumab study. At first, she had a tough time with the treatment and became more ill, but she eventually improved and then kept improving to the point that Tripathy was able to clear her to go on a vacation.

“She sent me this amazing picture of her scuba diving in Belize. And just a couple of months before that, she was so ill that I didn’t think she would even qualify for the study. To see someone who was so ill such a short time ago be able to send me a picture from vacation was a really special moment for me,” he said.

BALANCING RESEARCH AND CARE

Tripathy developed a passion for science and medicine at a very early age by observing his father, who was an investigator and a physician. “When I was young, between 8 and 10 years old, I used to go to the lab with my father and help wash the glassware and do other simple tasks. I was just fascinated with all the experiments. And I also got to accompany him on house calls when he thought it was safe for me to go. So I sort of got to see the whole picture at a young age,” Tripathy told OncLive® in a recent interview.

Like his father, he has been able to structure his time so that he can engage in research activities as well as care for his patients in a way that allows him to maintain a personal touch. “I didn’t want to be trapped in just the cold science part or have a super busy clinician type of experience either,” he said.

Today, he says he has the best of both worlds, maintaining 1 or 2 clinic days and then spending the remainder of his time on research, teaching, and administration. This balance has enabled him to get to know his patients and keep in tune with their needs while also participating...
in the cutting-edge research that is expanding their treatment options and helping move the field forward.

Trastuzumab was among the first targeted therapies approved for cancer therapy. Tripathy has continued identifying and studying new drug targets that will personalize care. In 2014, he became the global principal investigator of the phase 3 MONALEESA-7 trial (NCT02278120) assessing ribociclib (Kiisqali), an orally bioavailable, selective CDK 4/6 inhibitor, as first-line therapy for premenopausal and perimenopausal patients with advanced hormone receptor-positive, HER2-negative breast cancer. Four years later, Tripathy and colleagues reported a progression-free survival (PFS) improvement in patients with the addition of ribociclib to endocrine therapy.1

“We were really excited when those data came out because we had broken the survival barrier that really hadn’t been crossed in hormone receptor-positive breast cancer. Being part of that story was very exciting,” he said.

MONALEESA-7 included 672 patients in the intention-to-treat (ITT) population and randomly assigned them to receive ribociclib or placebo in addition to endocrine therapy (goserelin plus a nonsteroidal aromatase inhibitor [AI] or tamoxifen).1 At 42 months, 70.2% of patients in the ribociclib arm were alive versus 46.0% of patients in the placebo arm, indicating a 29% reduction in the relative risk of death compared with placebo (HR, 0.71; 95% CI, 0.54-0.95; P = .00973). In the subgroup of 495 patients who received an AI, the overall survival (OS) benefit was consistent with that of the overall ITT population (HR for death, 0.70; 95% CI, 0.50-0.98).3

In July 2018, based on favorable PFS data from the MONALEESA-7 trial, the FDA expanded ribociclib’s indication for use in combination with an AI as an initial endocrine-based therapy in pre/perimenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.3 In March 2017, ribociclib had received its initial FDA approval for use in combination with an AI as an initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer, based on data from the MONALEESA-2 study (NCT01958021).4 Ribociclib also is approved in combination with fulvestrant (Faslodex) for postmenopausal women or in men with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine-based therapy or following disease progression on endocrine therapy.7

Looking forward, Tripathy sees several areas of the breast cancer treatment landscape on the cusp of change. In a wide-ranging interview with OncologyLive®, Tripathy discussed key developments that may set the stage for next directions in care.

### FINDING TARGETS, ADAPTING THERAPY
The cancer treatment paradigm has traditionally been based on killing as many cancer cells as possible. Although this approach is curative for some patients, others develop resistance mechanisms that eventually stop once-beneficial treatments from working, often leaving them in a treatment void.

“Just like rivers continue to flow downward under the force of gravity and form the landscape, we know that tumors do that, too, under selective pressure—just like gravity, they find a path. They are in continual evolution, and we have increasingly better tools to discern what new mutations are being acquired, to understand how that cancer is surviving,” Tripathy said. He explained that an evolving concept in cancer medicine is to use the information gleaned from new technologies, such as liquid biopsies, to adapt patients’ treatments in real time so that they stay ahead of their tumors’ evolving resistance mechanisms. He believes a proactive, rather than a reactive, approach will become the new treatment paradigm.

“If we can understand the mechanisms of resistance and be able to monitor patients in real time, then we will be able to turn many cases of cancer into chronic diseases. Hopefully, [they will be] chronic conditions that allow patients to experience a generally good quality of life,” he said.

To adapt a patient’s treatment requires an understanding of the nature of that patient’s tumor profile, including whether they have any beneficial, harmful, or neutral mutations so that therapies targeting potentially actionable mutations can be identified and used for treatment planning. Recently, mutations in the ESR1 gene, which encodes for an estrogen receptor (ER), have been found to be a common cause of acquired resistance to endocrine therapy in patients with metastatic ER-positive breast cancer. This discovery spurred the development of novel therapies to target these mutations, including potent selective ER degraders (SERDs) or modulators (SERMs) such as lasofoxifene (Fablyn), which Tripathy is studying. The SERD elacestran was shown to be more effective than the current standard, fulvestrant, especially in cases with ESR1 mutations, in findings of the EMERALD trial (NCT03778931) presented at the 2021 San Antonio Breast Cancer Symposium (SABCS 2021).8

Lasofoxifene is being investigated in combination with the CDK4/6 inhibitor abemaciclib (Verzenio) in the phase 2 ELAINEII trial (NCT04432454) in patients with advanced or metastatic ER-positive, HER2-negative breast cancer whose tumors harbor an ESR1 mutation. The trial completed enrollment in June 2021, and initial data are expected in the first half of 2022.9

Tripathy noted that the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH). Molecular Analysis for Therapy Choice; MMR, mismatch repair; NCI, National Cancer Institute.

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Choice (MATCH) Screening Trial (NCT02465060) is providing significant assistance in advancing adaptive therapy. It is one of the first trials to match patients with cancer to a treatment based on genetic changes in their tumors rather than their cancer type. NCI-MATCH plans to enroll more than 6000 patients with advanced refractory solid tumors, lymphomas, or myelomas who have progressed on standard treatment and harbor certain genetic changes into 1 of more than 35 subprotocol studies, with most arms planning to enroll approximately 35 patients. Ten substudies in NCI-MATCH are currently open for enrollment (Table 1).

Findings from various NCI-MATCH substudies have confirmed that targeting genetic changes in tumors, such as mutations, amplifications, and fusions, is an effective strategy and that genomic sequencing in patients with advanced cancers may be beneficial in guiding treatment decision-making.11 “We’re sequencing everyone at MD Anderson with metastatic breast cancer because we may find a rare mutation that’s got a drug approved for it or in clinical trials, regardless of where the tumor originated,” Tripathy said.

NCI-MATCH data have led to plans for other large NCI basket trials such as ComboMATCH, which will test genomically directed combination regimens; MyeloMATCH, which will assign therapy for patients with acute myeloid leukemia and myelodysplastic syndromes based on genetic changes in their cancer cells; and ImmunoMATCH, which will use immune profiling to channel patients to treatments based on tumor mutational burden and interferon signature.11,12 Tripathy expressed excitement about the PI3K/AKT pathway, a signal transduction pathway that was successfully targeted in the NCI-MATCH trial.

The PI3K/AKT pathway is one of the most frequently altered pathways in cancer, including genetic changes such as aberrant signaling, overexpression, sequence variations, and somatic copy number alterations. In the EAY131-Y subprotocol of the NCI-MATCH trial, 35 patients with ERBB2 E17K-mutated metastatic tumors of various histologies were treated with capivasertib, an AKT inhibitor, at 480 mg orally twice daily for 4 days on and 3 days off weekly in 28-day cycles until disease progression or unacceptable toxicity. In patients with metastatic breast cancer who continued hormone therapy, capivasertib was reduced to 400 mg.13 The most prevalent cancers treated included patients with breast (n=18) and gynecologic (n=11) malignancies. The overall response rate across cancer types was 28.6% (95% CI, 15.4-46.2%). One patient with endometrioid endometrial adenocarcinoma achieved a complete response and was still receiving treatment at 35.6 months. Nine patients had partial responses and continued to receive treatment at 28.8 months, which included 7 patients with hormone receptor-positive/HER2-negative breast cancer, 1 with uterine leiomyosarcoma, and 1 with oncocytic parotid gland carcinoma.13 Several trials are open at MD Anderson that target different components of this critical pathway both for breast and other cancers.

Tripathy expects data for several key trials focused on the AKT pathway to be released in 2022, including a follow-up trial of the EAY131-Y subprotocol with capivasertib. He also anticipates follow-up data from the phase 1/2 FAKTION trial (NCT01992952). The initial FAKTION trial data showed a nearly 6-month PFS improvement when capivasertib vs placebo was added to fulvestrant in women with advanced ER-positive/HER2-negative breast cancer (median PFS, 10.3 vs 4.8 months, respectively).13

Based on these promising initial data, the phase 3 trial CAPItello-291 trial (NCT04305496) is currently recruiting patients. Investigators plan to enroll more than 800 patients with locally advanced or metastatic triple-negative breast cancer in the randomized, double-blinded, phase 3 CAPItello-290 trial (NCT03997123), where capivasertib vs placebo is being added to paclitaxel. This trial is seeking to enroll more than 900 patients and has an estimated primary completion date of May 2022. Additionally, capivasertib is being studied as first-line therapy for women with locally advanced or metastatic triple-negative breast cancer in the randomized, double-blinded, phase 3 CAPItello-290 trial (NCT03997123), where capivasertib vs placebo is being added to paclitaxel. This trial is seeking to enroll more than 900 patients and has an estimated primary completion date of March 2023.

FINDING THERAPIES FOR TUMORS WITH LOW EXPRESSION OF TARGETABLE BIOMARKERS

For a tumor to be considered positive for a targetable biomarker, it must express a certain quantity of that biomarker, which is usually set at fairly high levels. It has been discovered, however, that such tumors may still express very low levels of the targetable biomarker, which may render them vulnerable to a treatment targeting that biomarker if a potent enough treatment is found.

This is the story that is now unfolding with HER2-positive breast cancers. Although patients with HER2-positive breast cancers historically have had a lower likelihood of cure and survival, this changed with the advent of HER2-targeted therapies, including trastuzumab. Until recently, however, only patients with strong HER2 expression could be treated with such agents, but Tripathy said that may soon change.

He noted the development of fam-trastuzumab deruxtecan-nxki (Enbrelux), a HER2-directed antibody-drug conjugate currently approved for patients with previously treated unresectable or metastatic breast cancer and for those with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction cancer.

TRIPATHY, CONTINUED ON PAGE 26
Learn how to use state-of-the-art breast cancer care strategies to optimize patient outcomes.

In March 2022, the 39th Annual Miami Breast Cancer Conference® will continue the tradition of providing value to attendees and enabling you to integrate the highest-quality methodologies into your clinic.

Using innovative virtual technology to deliver robust educational programming and top-notch presentations, next year’s program will feature world-class tumor board panels, multidisciplinary meet-the-expert sessions, poster talks, and lively debates to improve the care of patients with breast cancer.

“All of the presenters were effective in presentation and knowledge base. This meeting is so important for my practice.”
—2021 Attendee
Looking Ahead to the 39th Annual Miami Breast Cancer Conference®

Since the mid-1980s, the Miami Breast Cancer Conference® has provided an opportunity for breast cancer specialists from all disciplines to learn about emerging therapeutic strategies that they can translate into clinical practice. This year’s conference will fulfill that mission as a combined virtual and live meeting, Physicians’ Education Resource® (PER™), LLC, is hosting the 39th Annual Miami Breast Cancer Conference® Thursday, March 3, through Sunday, March 6, 2022, at Fontainebleau Miami Beach in Florida. Some faculty and attendees will join the meeting remotely.

“This actually allows us to have a larger faculty, an international faculty,” said Debu Tripathy, MD, professor and chair of the Department of Breast Medical Oncology, Division of Cancer Medicine, at the University of Texas MD Anderson Cancer Center in Houston. Tripathy is a longtime leader of the Miami Breast Cancer Conference®.

Patrick I. Borgen, MD, chair of the Department of Surgery at Maimonides Medical Center in Brooklyn, New York, serves as chair of the conference. Joining Tripathy as cochairs of the meeting are Anees Chagpar, MD, MSc, MPH, MA, MBA, FACS; and Hope S. Rugo, MD, FASCO. Chagpar is a professor in the Department of Surgery at Yale School of Medicine in New Haven, Connecticut. Rugo, a 2020 Giants of Cancer Care® award winner in the education category, is director of Breast Oncology and Clinical Trials Education and a professor of medicine at University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center.

Over its 4-day course, the meeting will cover many important topics in breast cancer. Tripathy said a key area of focus will be on adaptive therapies and personalization of therapies, with discussions covering recent innovations, such as developments on the immunotherapy front and with newer targeted agents, including use of selective estrogen receptor downregulators, PARP inhibitors, and antibody-drug conjugates (Table). There will also be many practical sessions focused on care issues such as use of neoadjuvant chemotherapy, treatment-related toxicities (eg, cardiotoxicity), treatment sequencing, and imaging and cancer staging.

The conference will feature several patient speakers who will share their cancer journeys. Additionally, several hot-topic medical debates are planned. “We pick a controversial topic and have 2 people duke it out, but it’s all in good fun,” Tripathy said.

During the meeting, he will engage in a Medical Crossfire® debate with Sara A. Hurvitz, MD, medical director of the Jonsson Comprehensive Cancer Center Clinical Research Unit at UCLA in Los Angeles, California, on the use of adjuvant immune checkpoint inhibitors (ICIs) entitled “Adjuvant Immune Checkpoint Inhibitors: Yes or No.”

Table: Selected Conference Highlights: Sessions and Speakers

| Incorporating Immunotherapy into the Treatment of Early-Stage Breast Cancer—Hope Rugo, MD, FASCO, director of breast oncology and clinical trials education and a professor of medicine at University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center |
| Surgical Management of the Axilla in the Era of RxlPONDER and monarchE—Elizabeth A. Mittendorf, MD, PhD, director of the Breast Immuno-Oncology Program, Dana-Faber Cancer Institute; Rob and Karen Hale Distinguished Chair in Surgical Oncology, Brigham and Women’s Hospital |
| Emerging Data on Oral Selective Estrogen Receptor Degraders and Other Novel Hormonal Therapies—Aditya Bardia, MD, MPH, attending physician, medical oncology, Massachusetts General Hospital |
| Advances in the Treatment of Brain Metastases and Leptomeningeal Disease in HER2+ Breast Cancer—Mark Pegram, MD, associate director for clinical research, Stanford Comprehensive Cancer Institute |
| Therapeutic Sequencing for Metastatic HER2+ Breast Cancer: Where Are We Now? Where Are We Headed?—Sara M. Tolaney, MD, MPH, chief of the Division of Breast Oncology, Susan F. Smith Center for Women’s Cancers, Dana-Faber Cancer Institute |
| Primer in Genomics: Applications to the Clinic in 2022—Debu Tripathy, MD, chair, Department of Breast Medical Oncology, Division of Medicine, The University of Texas MD Anderson Cancer Center |
| Will a Bespoke ctDNA Panel Replace Pathological Response to Guide Management After Neoadjuvant Therapy?—Pat W. Whitworth Jr, MD, director of the Nashville Breast Center |
| Oncoplastic Considerations in Patients Receiving Radiotherapy After Neoadjuvant Therapy—Lloyd B. Gayle, MD, director of plastic surgery and vice chair of surgery, Maimonides Medical Center |
| Risk Stratification in Early-Stage Hormone Receptor–Positive Breast Cancer—Kevin Kalinsky, MD, MS, director of the Glenn Family Breast Center, Winship Cancer Institute of Emory University |

Inhibitor for a Patient With Pathological Complete Response After Neoadjuvant ICI Plus Chemotherapy: Yes or No.”

A key feature of the meeting is that it is multidisciplinary. “We have pathologists, radiologists, medical radiation [specialists], medical oncologists, and surgical oncologists all together. We believe that it takes a village,” Tripathy said.

He emphasized that the goal is for any physician treating a patient with breast cancer to know “the entire picture,” even if it is outside their area of specialty. “We want surgeons to know what’s going on in genomics, and we want the medical oncologist to know what is going on with latest surgical and radiation technologies and postoperative pain management. Basically, we want everybody who attends the conference to be able to go back to their office on Monday and be able to really communicate with their patients about the latest comprehensive and multidisciplinary treatment planning and how it may apply to them,” he said.
The findings in low HER2-expressing tumors from the DAISY study support those previously reported in 2020 in a subgroup analysis of a first-in-human, phase 1b study (NCT02564900) assessing trastuzumab deruxtecan, which showed an ORR of 37.0% among heavily pretreated patients with HER2 low-expressing advanced or metastatic breast cancers.20 The finding of a nearly 30% BOR in the DAISY trial among individuals with no detectable HER2 expression, however, has led to some questions, including whether those individuals may have HER2 expression levels below what current assays are able to detect. Another presentation from SABCS 2021 may lend support to that theory.21 According to an analysis of data from 1400 global laboratories, current standard assays measuring HER2 expression were not able to efficiently differentiate between HER2 expression levels of IHC0 and IHC1+. More studies are under way to understand the distinct biology in HER2-low breast cancers.

IMPROVING OUTCOMES IN PATIENTS WITH BRAIN METASTASES

The blood-brain barrier has long been difficult to cross. However, some newer agents are able to pass through this barrier and are potent enough to exert their effects on brain metastases, Tripathy said. In patients with HER2-positive breast cancer with brain metastases, one such agent is tucatinib (Tukysa).

In the HER22CLIMB trial (NCT02614794), 612 patients with HER2-positive breast cancer with and without brain metastases were randomized to receive tucatinib or placebo in combination with trastuzumab and capecitabine. Overall, 47.5% (n = 291) of the total population had brain metastases or without brain metastases were randomized to

trastuzumab and capecitabine. Overall, 47.5% (n = 291) of the total population had brain metastases or without brain metastases were randomized to

The median PFS was 7.8 months for patients who received the regimen containing tucatinib compared with 5.6 months for those who received placebo (HR for disease progression or death, 0.54; 95% CI, 0.42-0.71; P < .001). Findings were similar for patients with brain metastases; the median PFS was 7.6 months with tucatinib vs 5.4 months with placebo (HR, 0.48; 95% CI, 0.34-0.69; P < .001).21 In April 2020, the FDA approved the tucatinib regimen for patients with previously treated advanced unresectable or metastatic HER2-positive breast cancer based on findings from the study.22

New data presented at SABCS 2021 from an exploratory analysis of HER22CLIMB results showed that adding tucatinib to trastuzumab and capecitabine in patients with active and stable brain metastases improved the median OS by 20.5% for those treated with T-DM1.23 “We’re at the point now where [individuals] with brain metastases can live for many years. Now the next barrier to cross is going to be treating non-HER2-positive brain metastases,” Tripathy said.

He noted that several agents are being examined that may provide benefit to patients with brain metastases without HER2-positive tumors, including sacituzumab govitecan-hziy (Trodelyn). The FDA, which initially approved the drug on an accelerated basis in April 2020, granted regular approval the following year for patients with unresectable locally advanced or metastatic triple-negative breast cancer previously treated with 2 or more prior systemic therapies, at least 1 of which was for metastatic disease.24 The regular approval was based on data from the phase 3 ASCENT trial (NCT02574455), which included patients with and without brain metastases.

Among all randomized patients, median PFS in the sacituzumab govitecan plus chemotherapy arm was 4.8 months (95% CI, 4.1-5.8) compared with 1.7 months (95% CI, 1.5-2.5) in those receiving chemotherapy alone (HR, 0.43; 95% CI, 0.35-0.54; P < .0001). Median OS was 11.8 months (95% CI, 10.5-13.8) and 6.9 months (95% CI, 5.9-7.6), respectively (HR, 0.51; 95% CI, 0.41-0.62; P < .0001).24 Studies assessing sacituzumab govitecan in CNS metastases are under way.

EXPLORING IMMUNOCENICITY

Cancer stem cells (CSCs) were discovered in leukemia in the mid-1990s.25 Since their discovery, they have been considered a promising therapeutic target. “Most cells have the capacity to move back into their stem state, and cancer cells do that to escape treatment,” Tripathy explained, adding that this leads to the cancer becoming less immunogenic.

Tripathy is working on a project exploring epithelial-mesenchymal transition (EMT), a complex gene expression program that enables cancer cells to suppress their epithelial features and change into mesenchymal/CSC-like ones, giving the cell mobility and the capacity to migrate from its primary site, which can lead to metastases. Using a proprietary platform called ApoStream that isolates circulating tumor cells (CTCs) for research use, Tripathy and colleagues were able to detect chemotherapy-resistant micrometastatic disease expressing an EMT-like or CSC-like phenotype in the neoadjuvant setting. The presence of EMT-CTCs or CSC-CTCs was not predictive, however, of tumor response to neoadjuvant chemotherapy.26

FOCUSING ON FIELD OF CANCER ENERGETICS

“Cancer cells are highly metabolic and programmed to focus their functions primarily on growth, which requires more energy,” Tripathy said. This understanding has given rise to the field of cancer energetics, which focuses on understanding how cancer cells derive their energy so that their metabolic pathways may become targets for anticancer therapies.

Several important observations have been made in cancer energetics since the 1920s when Otto Warburg, a German physician and Nobel laureate, observed that cancer cells consume more glucose and produce more lactate than normal cells and suggested that cancer cells rely on adenosine triphosphate (ATP) production via the glycolytic pathway to satisfy their energy requirements.27,28 More recent observations suggest a metabolic symbiosis, with glycolytic and oxidative tumor cells mutually regulating their energy metabolism. Hypoxic cancer cells use glucose for glycolytic metabolism and release lactate. Oxygenated cancer cells then use that lactate as fuel.

“Our bodies also have their own macro level type of energy generation that has a lot to do with our quality of life and whether we gain or lose weight and our energy levels or sleep states. So at that level, understanding the biology of energetics has a whole different meaning,” Tripathy said. At MD Anderson teams are working on both the macro and micro sides of cancer energetics, which is an area of research that he also is actively involved with and one that he sees leading to promising developments in the near future.

Much of the cancer metabolism research is being done in the Gan Laboratory.29 Areas of focus include the role and mechanisms of ferroptosis, an iron-dependent, nonapoptotic form of regulated cell death involving lipid peroxidation, cellular metabolism, tumor suppression, and cancer therapy, as well as cystine metabolism-induced nutrient dependency and its implication in cancer therapy. The hope is that a better understanding of ferroptosis and nutrient dependency will translate into novel efficacious cancer therapies. In June 2021, investigators from the Gan Laboratory published preclinical findings pointing to a possible target, dihydroorotate dehydrogenase (DHODH), with DHODH inhibitors in GPX4- cancers being a potential strategy to inhibit ferroptosis and lead to cancer cell death.30

For a full list of references, see the article at OncLive.com
FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

BLENREP is the first and only BCMA-targeted ADC monotherapy. So you can offer your RRMM patients a different option.

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

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

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

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

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

Learn more at BLENREPHCP.com
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Ocular Toxicity: Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and 14% had follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 14%. Decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Advertise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose.

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

ADVERSE REACTIONS
The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.14 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
The following is a brief summary only; see full Prescribing Information for complete product information.

**WARNING: OCULAR TOXICITY**

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

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

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

**1 INDICATIONS AND USAGE**

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

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

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Ocular Toxicity**

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

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

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

**Monitoring and Patient Instruction**

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

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

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

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

**5.2 BLENREP REMS**

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

Notable requirements of the BLENREP REMS include the following:

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

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

**5.3 Thrombocytopenia**

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 15%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient.

Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

**5.4 Infusion-Related Reactions**

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

**5.5 Embryo-Fetal Toxicity**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

**6 ADVERSE REACTIONS**

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

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

**6.1 Clinical Trials Experience**

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

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

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 99). Among these patients, 22% were exposed for 6 months or longer.

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

Serious adverse reactions in >3% of patients included pneumonia (9%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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

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

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (9%).

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

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

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

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

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.
† Visual acuity changes were determined upon eye examination.
‡ Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
§ Dry eyes included dry eye, ocular discomfort, and eye pruritus.
¶ Fatigue included fatigue and asthenia.
Six infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthma, hypertension, lethergy, and tachycardia.

Clinically relevant adverse reactions in <10% of patients included:
- **Eye Disorders:** Photophobia, eye irritation, infective keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders:** Vomiting.
- **Infections:** Pneumonia.
- **Investigations:** Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP (N = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2,774 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blfm, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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

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

**Data**

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

(continued on next page)
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

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

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

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

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

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Elacestrant Significantly Improves PFS in Advanced ER+, ESR1-Mutant Breast Cancer

by GINA MAURO

THE SELECTIVE ESTROGEN RECEPTOR degrader (SERD) elacestrant (RAD1901) led to a 30% reduction in the risk of disease progression or death compared with standard of care (SOC) in patients with estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer who previously received CDK4/6 inhibition. Investigators presented results of the phase 3 EMERALD trial (NCT03778931) at the 2021 San Antonio Breast Cancer Symposium.1

Specifically, data showed that the median progression-free survival (PFS) by independent review was 2.79 months with elacestrant and 1.91 months with standard therapy in the intention-to-treat population (ITT; HR, 0.697; 95% CI, 0.552-0.880; P = .0018).

In a subgroup of patients with ESR1 mutations, elacestrant was linked with a median PFS of 3.78 months vs 1.87 months with standard therapy, leading to a 45% reduction in the risk of disease progression or death in this subgroup (HR, 0.546; 95% CI, 0.387-0.768; P = .0005).

Elacestrant is the first oral SERD that blocks the ER in a dose-dependent manner that has previously shown clinical activity in postmenopausal women with ER-positive, HER2-negative metastatic breast cancer.2,3 In the phase 3 EMERALD trial, investigators randomized 477 men and postmenopausal women with advanced or metastatic ER-positive, HER2-negative breast cancer to receive elacestrant at 400 mg daily (n = 239) or investigator’s choice of SOC with fulvestrant, anastrozole, letrozole, or exemestane (n = 238). Patients must have progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6 inhibitor, had 1 or fewer lines of chemotherapy for advanced disease, and had an ECOG performance status of 0 or 1.

Treatment was given until progressive disease or withdrawal. The coprimary end points were PFS in the overall population and in those with ESR1 mutations. Overall survival (OS) was a secondary end point. Patients were stratified by ESR1-mutation status, prior fulvestrant, and visceral metastases.

A total 91.6% of patients discontinued elacestrant compared with 93.7% of those who discontinued standard of care. Most patients discontinued elacestrant because of disease progression per investigator (84.5%), adverse effect (AE; 2.1%), withdrawal of consent (2.5%), or investigator’s decision (2.5%).

Additional data showed that in all patients, the 6-month PFS rate was 34.3% (95% CI, 27.2%-41.5%) with elacestrant vs 20.4% (95% CI, 14.1%-26.7%) with SOC. At 12 months, the PFS rate was 22.32% (95% CI, 15.24%-29.40%) compared with 9.42% (95% CI, 4.02%-14.81%), respectively (TABLE 1).1

In patients with ESR1-mutant disease, the 6-month PFS rate with elacestrant was 40.8% (95% CI, 30.1%-51.4%) vs 19.1% (95% CI, 14.1%-26.7%) with SOC. The 12-month PFS rates were 26.7%
Outcomes demonstrated a significant improvement in patients treated with elacestrant in both the ITT population and the ESR1-mutant population (Table 2).

“Here you see a direct comparison between an oral SERD and an intramuscular SERD,” Bardia said. “Again, the benefit with elacestrant was higher as compared with a hazard ratio of 0.684 overall and 0.504 in those with mutations, and this was significant.”

At an interim analysis, the median OS was not calculated in either arm but favored elacestrant in both the ITT (HR, 0.751; 95% CI, 0.542-1.038; P = .0821) and ESR1-mutant population (HR, 0.592; 95% CI, 0.361-0.958; P = .0325).

“Although no statistically significant differences were noted in OS, an evident trend favoring elacestrant was noted in both groups,” Bardia said, adding that the final analysis is expected to take place in late 2022 or early 2023.

Regarding safety, the most common all-grade treatment-emergent AEs (TEAEs) with elacestrant and SOC included nausea (25.3% vs 18.8%, respectively), fatigue (19.0% vs 18.8%), vomiting (19.0% vs 8.3%), decreased appetite (14.8% vs 9.2%), and arthralgia (14.3% vs 16.2%). Grade 3/4 TEAEs included nausea (2.5% vs 0.9%, respectively), back pain (2.5% vs 0.4%), and increased alanine aminotransferase (2.1% vs 0.4%). No treatment-related deaths occurred in either arm.

Elacestrant was well tolerated with a predictable and manageable safety profile consistent with other endocrine therapies,” Bardia said. Bardia concluded that elacestrant in combination with targeted therapies, including CDK4/6 and mTOR inhibitors, is being studied in earlier lines of treatment in ongoing trials of patients with ER-positive, HER2-negative breast cancer.

“Clinically, elacestrant has the potential to become the new standard of care in the studied patient population,” Bardia said.

Carlos Arteaga, MD, FAACR, director of the Harold C. Simmons Comprehensive Cancer Center and the Lisa K. Simmons Distinguished Chair in Comprehensive Oncology at The University of Texas Southwestern Medical Center in Dallas, commented on the findings during the press briefing.

“The results clearly suggest that this new SERD may be a new treatment option for patients with breast cancer, not only as a single therapy, but also in combination with other targeted therapies,” Arteaga said.

REFERENCES

Table 1. Primary Outcomes of the EMERALD Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elacestrant (n = 239)</th>
<th>Standard of care (n = 238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>2.79</td>
<td>1.91</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>34.3% (27.2%-41.5%)</td>
<td>20.4% (14.1%-26.7%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>22.3% (15.2%-29.4%)</td>
<td>9.4% (4.0%-14.8%)</td>
</tr>
<tr>
<td>Patients with ESR1 mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Elacestrant (n = 115)</td>
<td>Standard of care (n = 113)</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>3.78</td>
<td>1.87</td>
</tr>
<tr>
<td>6-month PFS rate (95% CI)</td>
<td>40.8% (30.1%-51.4%)</td>
<td>19.1% (14.1%-26.7%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>26.8% (16.2%-37.4%)</td>
<td>8.2% (1.3%-15.1%)</td>
</tr>
<tr>
<td>PFS, progression-free survival</td>
<td></td>
<td></td>
</tr>
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</table>

Table 2. Analysis of Patients Treated With Fulvestrant in EMERALD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elacestrant (n = 239)</th>
<th>Fulvestrant (n = 165)</th>
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</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>2.79 (1.94-3.78)</td>
<td>1.94 (1.87-2.10)</td>
</tr>
<tr>
<td>Patients with ESR1 mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Elacestrant (n = 115)</td>
<td>Fulvestrant (n = 83)</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.78 (2.17-7.26)</td>
<td>1.87 (1.84-2.10)</td>
</tr>
<tr>
<td>PFS, progression-free survival</td>
<td></td>
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</tr>
</tbody>
</table>
Trastuzumab Deruxtecan Stands Out as Second-line Standard in HER2+ Metastatic Breast Cancer

by CAROLINE SEYMOUR

TREATMENT WITH FAM-TRASTUZUMAB deruxtecan-nxki (Enhertu) resulted in prolonged progression-free survival (PFS) and higher responses vs ado-trastuzumab emtansine (T-DM1; Kadcyla) as a second-line therapy in patients with HER2-positive metastatic breast cancer. Findings from an exploratory analysis of the phase 3 DESTINY-Breast03 trial (NCT03529110) presented at the 2021 San Antonio Breast Cancer Symposium support the use of the antibody-drug conjugate across all patient subgroups, including those with baseline brain metastases.1 At a median follow-up of 15.9 months, the median PFS for patients with brain metastases at baseline was 15.0 months (95% CI, 12.5-22.2) with trastuzumab deruxtecan (n = 43) vs 3 months (95% CI, 2.8-5.8) with T-DM1 (n = 39; HR, 0.25; 95% CI, 0.13-0.45). The 12-month PFS rates were 72% (95% CI, 55%-83.5%) vs 20.9% (95% CI, 8.7%-36.6%), respectively.

The median PFS was not estimable (NE; 95% CI, 22.2-NE) among the 218 patients without brain metastases at baseline treated with trastuzumab deruxtecan vs 7.1 months (95% CI, 5.6-9.7) with T-DM1 (n = 224; HR, 0.30; 95% CI, 0.22-0.40). The 12-month PFS rates were 76.5% (95% CI, 70%-81.8%) compared with 36.4% (95% CI, 29.4%-43.4%), respectively.

"These data support [trastuzumab deruxtecan] becoming the standard of care for the second-line treatment of patients with HER2-positive metastatic breast cancer," Sara A. Hurvitz, MD, lead study author, said in a presentation of the data. Hurvitz is an associate professor at the David Geffen School of Medicine, medical director of the Jonsson Comprehensive Cancer Center Clinical Research Unit, codirector of the Santa Monica-UCLA Outpatient Oncology Practices, and director of the Breast Cancer Clinical Trials Program at UCLA in Los Angeles, California.

Investigators for the DESTINY-Breast03 trial, randomized 524 patients with HER2-positive metastatic breast cancer who had been previously treated with trastuzumab (Herceptin) and a taxane to receive either 5.4 mg/kg of trastuzumab deruxtecan every 3 weeks (n = 261) or 3.6 mg/kg of T-DM1 every 3 weeks (n = 263). Patients with clinically stable or treated brain metastases were eligible for enrollment. Baseline characteristics were comparable between the trastuzumab deruxtecan and T-DM1 arms: 50.2% vs 51% of patients had a positive hormone receptor, 23.8% vs 19.8% had a history of brain metastases, 16.5% vs 14.8% had baseline brain metastases, and 70.5% vs 70.3% had visceral disease, respectively. The median age was 54.3 years (range, 27.9-83.1) in the trastuzumab deruxtecan arm compared with 54.2 years (range, 20.2-83.0) in the T-DM1 arm.

Approximately half of the patients in each arm had received 1 prior line of therapy in the metastatic setting (50.6% in the trastuzumab deruxtecan arm; 47.9% in the T-DM1 arm). The percentages of patients who had received at least 2 prior lines of therapy were 49.4% vs 52.1%, respectively.

In the trastuzumab deruxtecan arm, 99.6% of patients had received prior trastuzumab and 62.1% of patients had received prior pertuzumab (Perjeta); in the T-DM1 arm, these rates were 99.6% and 60.1%, respectively.

The primary end point was PFS by blind independent central review (BICR). A key secondary end point was overall survival (OS); other secondary end points included objective response rate (ORR) by BICR and investigator review.

TABLE. Outcomes in Key Subgroups of DESTINY-Breast03

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Outcome</th>
<th>Trastuzumab deruxtecan</th>
<th>T-DM1</th>
</tr>
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<tbody>
<tr>
<td><strong>HR status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (n = 133)</td>
<td>Median PFS, months (95% CI)</td>
<td>22.4 (17.7-NE)</td>
<td>6.9 (4.2-9.8)</td>
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<tr>
<td>ORR</td>
<td>78.2%</td>
<td>30.9%</td>
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<tr>
<td>Negative (n = 126)</td>
<td>Median PFS, months (95% CI)</td>
<td>NE (18.0-NE)</td>
<td>6.8 (5.2-8.3)</td>
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<tr>
<td>ORR</td>
<td>81.7%</td>
<td>38.5%</td>
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<td><strong>Prior pertuzumab</strong></td>
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<tr>
<td>Yes (n = 162)</td>
<td>Median PFS, months (95% CI)</td>
<td>NE (18.5-NE)</td>
<td>6.8 (5.4-8.3)</td>
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<tr>
<td>ORR</td>
<td>79.6%</td>
<td>32.9%</td>
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<tr>
<td>No (n = 99)</td>
<td>Median PFS, months (95% CI)</td>
<td>NE (16.5-NE)</td>
<td>7.0 (4.2-9.7)</td>
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<tr>
<td>ORR</td>
<td>79.8%</td>
<td>36.2%</td>
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<tr>
<td><strong>Visceral disease</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Yes (n = 195)</td>
<td>Median PFS, months (95% CI)</td>
<td>22.2 (16.5-NE)</td>
<td>5.7 (4.2-7.0)</td>
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<tr>
<td>ORR</td>
<td>77.4%</td>
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<tr>
<td>No (n = 66)</td>
<td>Median PFS, months (95% CI)</td>
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<tr>
<td>ORR</td>
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<td><strong>Prior therapy</strong></td>
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<tr>
<td>0-1 (n = 132)</td>
<td>Median PFS, months (95% CI)</td>
<td>22.4 (17.9-NE)</td>
<td>8.0 (5.7-9.7)</td>
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<tr>
<td>ORR</td>
<td>75.0%</td>
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<tr>
<td>≥ 2 (n = 129)</td>
<td>Median PFS, months (95% CI)</td>
<td>NE (16.8-NE)</td>
<td>5.6 (4.2-7.1)</td>
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<tr>
<td>ORR</td>
<td>84.5%</td>
<td>32.8%</td>
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<tr>
<td><strong>Brain metastases</strong></td>
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<td></td>
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<tr>
<td>Yes (n = 43)</td>
<td>Median PFS, months (95% CI)</td>
<td>15.0 (12.5-22.2)</td>
<td>3.0 (2.6-5.8)</td>
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<tr>
<td>ORR</td>
<td>67.4%</td>
<td>20.5%</td>
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<tr>
<td>No (n = 218)</td>
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<td>NE (22.4-NE)</td>
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<tr>
<td>ORR</td>
<td>82.1%</td>
<td>36.6%</td>
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</tbody>
</table>

NE, not estimable; ORR, objective response rate; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine.
ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.¹⁻¹⁰

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.¹¹

INDICATION
RYBREVANT® (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Infusion-Related Reactions
RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range: 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipertotics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis
RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Reactions
RYBREVANT® can cause rash (including dermatitis acniform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
Results for tough-to-treat disease

- 3.7% of patients achieved a CR
- 36% of patients achieved a PR

**ORR**

40%

95% CI: 29%, 51%

(n=81)

- Efficacy was evaluated by ORR¹ and DOR¹

**MEDIAN DOR WAS 11.1 MONTHS**¹²

(95% CI: 6.9, NE)¹

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*CHRYSLIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYREVANT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR exon 20insertion mutations as determined by previous local standard of care testing, whose disease had progressed on or after platinum-based chemotherapy. RYREVANT® was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.¹²

*According to Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) as evaluated by blinded independent Central Review (bICR).¹²

*Based on Kaplan-Meier estimates.¹²

The safety of RYREVANT® was evaluated in the CHRYSLIS® study (n=129)¹¹:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity¹¹

- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%)¹¹

- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%)¹¹

- IRRs occurred in 66% of patients treated with RYREVANT®, the majority of which may occur with the first infusion¹¹

¹Based on the safety population, N=302.

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The safety of RYREVANT® was evaluated in the CHRYSLIS® study (n=129)¹¹:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity¹¹

- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Please see Brief Summary of full Prescribing Information for RYREVANT® on subsequent pages.

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RYREVANT™ (amivantamab-vmjw) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved assay [see Dosage and Administration (2.1) in Full Prescribing Information], whose disease has progressed on or after platinum-based chemotherapy.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population [see Adverse Reactions], IRR occurred in 68% of patients treated with RYREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 93% were Grade 1 to 2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 82% and 1.3% of patients permanently discontinued RYREVANT due to IRR.

Premedicate with antihistamines, antiproteins, and glucocorticoids and infuse RYREVANT as recommended [see Dosage and Administration (2.3) in Full Prescribing Information] 15 minutes prior to administration via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.6) in Full Prescribing Information].

Monitor patients for any signs and symptoms of infusion reactions during RYREVANT infusion in a setting where cardiopulmonary resuscitation equipment and equipment are available. Interruption of infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Intestinal Lung Disease/Pneumonitis

RYREVANT can cause intestinal lung disease (ILD)/pneumonitis. Based on the safety population [see Adverse Reactions], ILD/pneumonitis occurred in 3.3% of patients treated with RYREVANT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (2.4) in Full Prescribing Information].

Dermatologic Adverse Reactions

RYREVANT can cause rash (including dermatitis acneform), pruritus, and dry skin. Based on the safety population [see Adverse Reactions], rash occurred in 74% of patients treated with RYREVANT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYREVANT was permanently discontinued due to rash in 0.7% of patients [see Adverse Reactions].

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYREVANT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Ocular Toxicity

RYREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population [see Adverse Reactions], keratitis

occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYREVANT. All events were Grade 1–2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryofetal development, embryolethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYREVANT. [see Use in Specific Populations].

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions [see Warnings and Precautions]
- Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions]
- Dermatologic Adverse Reactions [see Warnings and Precautions]
- Ocular Toxicity [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under various 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 population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYREVANT as a single agent in the CHRYSAIIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYREVANT, 36% were exposed for ≤6 months and 12% were exposed for >6 months or longer and were exposed for greater than one year. In the safety population, the most common (≥20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting, and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphorus, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYREVANT at the recommended dose in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertions who had previously progressed on or after platinum-based chemotherapy. Among patients who received RYREVANT, 44% were exposed for ≤6 months and 12% were exposed for greater than one year.

The median age was 62 years (range: 38 to 84 years); 61% were female; 55% were Asian; 39% were White; and 23% were Black; and 82% had baseline body weight <80 kg. Serious adverse reactions occurred in 30% of patients who received RYREVANT. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYREVANT in ≥1% of patients were pneumonia, IR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥3% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥2% of patients included rash and paronychia.

The most common adverse reactions (≥20%) were rash, IR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphorus, decreased potassium, increased glucose, increased gamma glutamyl transferase, increased γ-glutamyl transferase, and decreased sodium.
Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exen 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYREVANT in CHRYSAZIS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYREVANT (N=129)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td></td>
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</tr>
<tr>
<td>Rash</td>
<td>84</td>
<td>3.9</td>
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<tr>
<td>Pruritus</td>
<td>18</td>
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<tr>
<td>Dry skin</td>
<td>14</td>
<td>0</td>
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</tr>
<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Infusion related reaction</td>
<td>64</td>
<td>3.1</td>
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<tr>
<td>Fatigue</td>
<td>33</td>
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<td>Edema</td>
<td>27</td>
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<td>Paronychia</td>
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<td>Musculoskeletal and connective tissue disorders</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>Vascular disorders</td>
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<td>Hemorrhage</td>
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<td>Metabolism and nutrition disorders</td>
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</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

* Rash: acne, dermatitis, dermalitis acnelform, eczema, eczema astecotic, palmar-plantar erythrodysesthesia syndrome, pernix rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrosis
* Fatigue: asthenia, fatigue
* Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
* Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
* Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
* Dyspnea: dyspnea, dyspnea exertional
* Cough: cough, productive cough, upper airway cough syndrome
* Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
* Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
* Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
* Peripheral neuropathy: hypesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
* Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYREVANT included ocular toxicity, ILD pneumonitis, and toxic epidermal necrolysis (TEN).

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC With EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYREVANT in CHRYSAZIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYREVANT (N=129)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>79</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
<td>4.8</td>
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</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
<td>0</td>
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<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
<td>8</td>
<td></td>
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<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
<td>0</td>
<td></td>
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<tr>
<td>Decreased magnesium</td>
<td>27</td>
<td>0</td>
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<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

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

In CHRYSAZIS, 3 of the 286 (1%) patients who were treated with RYREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmw1 antibodies (one at 27 days, one at 59 days and one at 188 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYREVANT.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on the mechanism of action and findings in animal models, RYREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYREVANT in pregnant women or animal data to assess the risk of RYREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and postnatal death in animals (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data
Animal Data
No animal studies have been conducted to evaluate the effects of amivantamab-vmw1 on reproduction and fetal development; however, based on its mechanism of action, RYREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in
multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmiv has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivantamab-vmiv in human milk or its effects on the breastfeeding child. Because of the potential for serious adverse reactions from RYBREVENT in breast-fed infants, advise women not to breastfeed during treatment with RYBREVENT and for 3 months after the final dose.

Females and Males of Reproductive Potential

RYBREVENT can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVENT.

Contraception

Females

Advises females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVENT.

Pediatric Use

The safety and efficacy of RYBREVENT have not been established in pediatric patients.

Geriatric Use

Of the 129 patients treated with RYBREVENT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advises patients that RYBREVENT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions [see Warnings and Precautions].

Interstitial Lung Disease/Pneumonitis

Advises patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [see Warnings and Precautions].

Dermatologic Adverse Reactions

Advises patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVENT [see Warnings and Precautions]. Advise patients to apply alcohol-free emollient cream to dry skin.

Ocular Toxicity

Advises patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated [see Warnings and Precautions].

Paresthesia

Advises patients of the risk of paresthesia. Advise patients to contact their healthcare provider for signs or symptoms of parasthesia [see Adverse Reactions].

Embryo-Fetal Toxicity

Advises females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVENT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. [see Warnings and Precautions, Use in Specific Populations].

Lactation

Advises women not to breastfeed during treatment with RYBREVENT and for 3 months after the final dose [see Use in Specific Populations].

Product of Ireland

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1884
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cp-213278v1
assessment, duration of response by BICR, PFS by investigator assessment, and safety.

Primary results from the study presented during the 2021 European Society for Medical Oncology Congress demonstrated that the median PFS was not reached (95% CI, 18.5-NE) with trastuzumab deruxtecan vs 6.8 months (95% CI, 5.6-8.2) with T-DM1 in the overall population (HR, 0.28; 95% CI, 0.22-0.37; P = 7.8 × 10^-22). The 12-month PFS rate was 75.8% (95% CI, 69.8%-80.7%) vs 34.1% (95% CI, 27.7%-40.5%), respectively.

At data cutoff, 32.2% of patients in the trastuzumab deruxtecan arm and 58.9% of patients in the T-DM1 arm had progressive disease. The median OS was NE in both arms (HR, 0.36; 95% CI, 0.36-0.86; P = 0.007172). The 12-month OS rates were 94.1% (95% CI, 90.3%-96.4%) in the trastuzumab deruxtecan arm vs 85.9% (95% CI, 80.9%-89.7%) in the T-DM1 arm.

Moreover, the confirmed ORR was 79.7% (95% CI, 74.3%-84.4%) with trastuzumab deruxtecan vs 34.2% (95% CI, 28.5%-40.3%) with T-DM1 (P < 0.0001); the complete response (CR) rates were 16.1% vs 8.7%, respectively.

**RESPONSE DATA AND SAFETY ANALYSIS**

Updated findings demonstrated that the PFS and confirmed ORR data also favored trastuzumab deruxtecan across patient subgroups (TABLE), including hormone receptor status (positive vs negative), prior pertuzumab treatment (yes vs no), visceral disease (yes vs no), prior lines of therapy (0-1 vs ≥ 2), and brain metastases (yes vs no).1

“Over 67% of patients in each subgroup had an objective response with [trastuzumab deruxtecan], with most [patients in each subgroup] exceeding three-quarters of patients having an objective response,” Hurvitz said.

Among patients with brain metastases, the confirmed ORR was 67.4% (95% CI, 51.5%-80.9%) with trastuzumab deruxtecan, which comprised 2 CRs and 27 partial responses (PRs). Patients who received T-DM1 had an ORR of 20.5% (95% CI, 9.3%-36.5%) with no patients experiencing a CR; all responses were PRs.

Among patients without brain metastases, the confirmed ORR was 82.1% (95% CI, 76.4%-87.0%), with 40 patients achieving a CR and 139 achieving a PR. The ORR with T-DM1 was 36.6% (95% CI, 30.3%-43.3%), with 23 patients experiencing a CR and 39 experiencing a PR. Notably, patients with brain metastases experienced a lower rate of progressive disease with trastuzumab deruxtecan vs T-DM1, at 48.8% vs 69.2%, respectively.

The median duration of response was NE in the overall population and among patients without brain metastases. Among those with brain metastases, the median duration of response was 12.9 months (95% CI, 8.5-NE) with trastuzumab deruxtecan vs 7.2 months (95% CI, 2.8-NE) with T-DM1.

Regarding intracranial responses, the CR rate was 27.8% with trastuzumab deruxtecan vs 2.8% with T-DM1. The intracranial PR rates were 36.1% vs 30.6%, respectively. Trastuzumab deruxtecan also led to a lower rate of intracranial progressive disease vs T-DM1, at 2.8% vs 22.2%, respectively.

“These data regarding the intracranial objective response are very intriguing and exciting, but we need larger studies that are ongoing to look at the activity of trastuzumab deruxtecan in untreated and actively progressing brain metastases,” said Hurvitz, adding that currently, level 1 evidence exists only for tucatinib (Tukysa) as a treatment option for patients with brain metastases in need of second-line therapy.

Regarding safety, treatment-emergent adverse effects (TEAEs) occurred in 99.6% of patients on trastuzumab deruxtecan vs 95.4% of patients on T-DM1; grade 3 or greater TEAEs occurred in 52.1% vs 48.3%, respectively. Despite this, the exposure-adjusted incidence rates (EAIRs) were lower with trastuzumab deruxtecan vs T-DM1.

The median treatment duration was 14.3 months (range, 0.7-29.8) with trastuzumab deruxtecan vs 6.9 months (range, 0.7-25.1) with T-DM1. TEAEs leading to discontinuation occurred in 13.6% of patients who received trastuzumab deruxtecan vs 7.3% of patients on T-DM1, but EAIRs were comparable (0.12 vs 0.11, respectively).

Most TEAEs were hematologic or gastrointestinal in nature. With interstitial lung disease (ILD)/pneumonitis, any-grade events occurred in 10.5% of patients in the trastuzumab deruxtecan arm vs 1.9% of patients in the T-DM1 arm. Notably, no grade 4 or 5 drug-related ILD/pneumonitis occurred with trastuzumab deruxtecan.

Hurvitz concluded that investigators are in the process of collecting data on the site of first progression and central nervous system PFS, which will be presented at an upcoming medical meeting. ■

**REFERENCES**


Pembrolizumab Plus Chemotherapy Emerges as First-line Option for Metastatic TNBC With PD-L1 CPS of 10 or Higher

by COURTNEY MARABELLA

Pembrolizumab (Keytruda) Plus chemotherapy demonstrated a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) vs chemotherapy alone in patients with previously untreated, locally recurrent, inoperable, or metastatic triple-negative breast cancer (TNBC) who have a PD-L1 combined positive score (CPS) of 10 or higher, according to an update analysis from the phase 3 KEYNOTE-355 trial (NCT02819518) presented during the 2021 San Antonio Breast Cancer Symposium.1

Results showed that the combination of pembrolizumab and chemotherapy yielded a median OS of 23.0 months vs 16.1 months with chemotherapy alone in patients with a CPS of 10 or higher (HR, 0.73; 95% CI, 0.55-0.95; P = .0093). The 18-month OS rates were 58.3% with pembrolizumab vs 44.7% with placebo/chemotherapy.

Moreover, the median PFS elicited by the combination was 9.7 months vs 5.6 months in patients with a CPS of at least 10 (HR, 0.66; 95% CI, 0.50-0.88). The 12-month PFS rate was 39.1% with pembrolizumab and 23.0% with placebo/chemotherapy. Investigators concluded that PD-L1 CPS of at least 10 was found to be a reasonable cutoff to define the population of patients expected to derive the most benefit from this regimen.

“These results provide further support for pembrolizumab in combination with chemotherapy as the new standard-of-care treatment regimen for patients with locally recurrent, unresectable, or metastatic TNBC [with tumors expressing] a PD-L1 CPS of 10 or more,” lead study author Javier Cortés, MD, PhD, the head of breast cancer and gynecological cancers at Hospital Universitario Ramón y Cajal in Madrid, Spain, said in a presentation of the data.

Pembrolizumab is currently approved by the FDA for use in combination with chemotherapy for the treatment of patients with locally recurrent, unresectable or metastatic TNBC with tumors expressing PD-L1 (CPS ≥ 10) as determined by an FDA-approved test. The November 2020 approval was based on earlier findings of the KEYNOTE-355 trial.2

The findings showed that the addition of pembrolizumab to chemotherapy resulted in a statistically significant and clinically meaningful improvement in both PFS and OS vs chemotherapy alone as a first-line treatment for patients with metastatic TNBC with a PD-L1 CPS of 10 or more. However, no statistically significant benefit in PFS or OS was previously observed in a subgroup of patients with PD-L1 CPS of 1 or higher, and the benefit of the regimen was not tested in the intention-to-treat (ITT) population because of the prespecified testing strategy.

KEYNOTE-522 DESIGN

In the trial, investigators enrolled patients 18 years or older with central determination of TNBC and PD-L1 expression. Patients had to have previously untreated, locally recurrent, inoperable, or metastatic disease; de novo metastasis or completion of treatment with curative intent within 6 months of first disease recurrence; and an ECOG performance status of 0 or 1. Patients’ life expectancy had to exceed 12 weeks, and adequate organ function was required. Those with active central nervous system metastasis, active autoimmune disease, or previous treatment with systemic steroids were not eligible for enrollment.

Patients were randomized 2:1 to receive either intravenous (IV) pembrolizumab plus chemotherapy or placebo plus chemotherapy. Pembrolizumab was administered at a dose of 200 mg every 3 weeks. Chemotherapy regimens included the following:

- Nab-paclitaxel (Abraxane): 100 mg/m² IV on days 1, 8, and 15 of every 28-day cycle
- Paclitaxel: 90 mg/m² IV on days 1, 8, and 15 of every 28-day cycle
- Gemcitabine/carboplatin: 1000 mg/m²/area under the curve 2 on days 1 and 8 of every 28-day cycle

Furthermore, patients were stratified by chemotherapy regimen (taxane vs gemcitabine/carboplatin), PD-L1 tumor expression (CPS ≥ 1 vs CPS < 1), and prior treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes vs no).

Primary end points for the study included PFS and OS in the PD-L1 CPS of 10 or higher, PD-L1 CPS of 1 or higher, and in the ITT populations. Secondary end points included objective response rate, duration of response, disease control rate, and safety in all treated patients.

SUBGROUP ANALYSIS REVEALS CONSISTENT EFFICACY

In this analysis, investigators sought to assess outcomes in subgroups of patients by additional CPS cutoffs. Of the 847 total patients enrolled on the study, 566 were randomized to the pembrolizumab group compared with 281 to the placebo group.

A total of 219 patients treated with pembrolizumab had a PD-L1 CPS of 10 or higher; 421 patients who were treated had a PD-L1 CPS of 1 or higher, and 562 were treated in the ITT population. Twenty-seven patients with a PD-L1 CPS of 10 or higher completed treatment and 189 discontinued, 35 patients with a PD-L1 CPS of 1 or higher completed treatment and 379 discontinued, and 39 patients in the ITT population completed treatment and 514 discontinued.

Among the 281 patients randomized to placebo, 103 were treated with a PD-L1 CPS of 10 or higher, 211 were treated with a PD-L1 CPS of 1 or higher, and 281 were treated in the ITT population. Five patients with a PD-L1 CPS of 10 or higher completed treatment and 95 discontinued, 8 patients with a PD-L1 CPS of 1 or higher completed treatment and 200 discontinued, and 12 patients in the ITT population completed treatment and 264 discontinued.

Baseline characteristics between the 2 treatment arms were well balanced. The median age was 53 years (range, 22-85), and 41.0% and 38.4% of patients on pembrolizumab and placebo, respectively, had an ECOG performance status of 1. Additionally, 75.1% of patients in each arm had a PD-L1 CPS of 1 or more; 38.9% and 36.7% of patients receiving pembrolizumab and placebo, respectively, had a PD-L1 CPS of 10 or higher.

Furthermore, more than half of patients in each arm received gemcitabine/carboplatin at 54.9% vs 53.5%.

OS Data

Additional data showed that, at a median follow-up of 44.0 months with pembrolizumab, the median OS in the group with PD-L1 CPS of 1 or higher was 17.6 months with pembrolizumab vs 16.0 months with placebo (HR, 0.86; 95% CI, 0.72-1.04; P = .0563) and 17.2 months vs 15.5 months, respectively, in the ITT population (HR, 0.89; 95% CI, 0.75-1.05). The 18-month PFS rates with pembrolizumab in the PD-L1 CPS of 1 or higher and ITT groups were 48.4% and 47.8%, respectively; in the placebo groups, these rates were 41.4% and 41.8%, respectively.
Further analyses showed that the median OS for pembrolizumab vs placebo was 16.2 months vs 14.7 months, respectively, in those with a PD-L1 CPS of less than 1 (HR, 0.97; 95% CI, 0.72-1.32); 13.9 months vs 15.5 months in those with a CPS of 1 to 9 (HR, 1.09; 95% CI, 0.85-1.40); 20.3 months vs 17.6 months in those with a CPS of 10 to 19 (HR, 0.71; 95% CI, 0.46-1.09); and 24.0 months vs 15.6 months in those with a CPS of 20 or higher (HR, 0.72; 95% CI, 0.51-1.01).

**PFS Data**

At a data cutoff date of June 15, 2021, the median PFS among those with a PD-L1 CPS of 1 or higher was 7.6 months in the pembrolizumab group vs 5.6 months in the placebo arm (HR, 0.75; 95% CI, 0.62-0.91); the 1-year PFS rates were 31.7% and 19.4%, respectively. In the ITT population, the median PFS was 7.5 months vs 5.6 months, respectively (HR, 0.82; 95% CI, 0.70-0.98), and the 1-year PFS rates were 29.3% and 20.8%.

When broken down further, the median PFS for pembrolizumab vs placebo was 6.3 months vs 6.2 months, respectively, in those with a PD-L1 CPS of less than 1 (HR, 1.09; 95% CI, 0.78-1.52), 5.7 months vs 5.6 months in those with a CPS of 1 to 9 (HR, 0.85; 95% CI, 0.65-1.11), 9.9 months vs 7.6 months in patients with a CPS between 10 and 19 (HR, 0.70; 95% CI, 0.44-1.09), and 9.2 months vs 5.4 months in those with a CPS of 20 or higher (HR, 0.62; 95% CI, 0.44-0.88).

**Safety Analysis**

In terms of safety, 96.3% of patients on pembrolizumab vs 95.0% of patients on placebo reported treatment-related adverse effects (TRAEs) of any grade; 68.1% vs 66.9%, respectively, had TRAEs reported as grade 3 to 5 in severity. Serious TRAEs occurred in 17.8% of patients on pembrolizumab vs 12.1% of those on placebo, and 18.3% vs 11.0% of patients, respectively, experienced a TRAE that led to discontinuation of either study drug. Moreover, 0.4% of patients on the pembrolizumab arm experienced a TRAE that led to death.

The most common TRAEs reported on the pembrolizumab and placebo arms were anemia (49.1% vs 45.9%, respectively), neutropenia (41.1% vs 38.1%), and nausea (39.3% vs 41.3%).

Immune-mediated AEs (imAEs) were reported in 26.5% of patients in the pembrolizumab arm vs 6.4% of those on placebo. Additionally, 5.3% of patients on pembrolizumab experienced an imAE that was grade 3 to 5 in severity, 3.4% reported serious imAEs, and 2.8% had an imAE that led to treatment discontinuation; these rates were 0% on the placebo arm.

**REFERENCES**


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**Datopotamab Deruxtecan Produces Encouraging Clinical Activity in Advanced TNBC**

by **CHRIS RYAN**

**DATOPOTAMAB DERUXTECAN (DATO-DXD)** showed durable overall response rates (ORR) in patients with advanced or metastatic triple-negative breast cancer (TNBC), according to data from the phase 1 TROPION-PanTumor01 trial (NCT03401385 presented at the 2021 San Antonio Breast Cancer Symposium).

Among all patients in the TNBC cohort (n = 44), the ORR by blinded independent central review was 34% (n = 15) at a median follow-up of 7.6 months (range, 4-13). This included a confirmed complete response (CR) or partial response (PR) in 14 patients (32%), plus 1 patient (2%) with a CR/PR that was pending confirmation. Seventeen patients (39%) had stable disease (SD), 2 patients (5%) were not evaluable (NE), and 8 patients (18%) had progressive disease (PD). Overall, the disease control rate (DCR) was 77%.

Furthermore, at a median follow-up of 8.8 months (range, 4-13), the ORR was 52% (n = 15) in patients with TNBC who did not receive prior treatment or in patients who had prior treatment with a Topo I inhibitor-based antibody-drug conjugate (ADC; n = 27), which included 13 patients (48%) with confirmed CRs or PRs, plus 1 patient (4%) with a CR/PR pending confirmation **[TABLE]**. Nine patients (33%) had SD, 1 patient (4%) was NE, and 4 patients (15%) had PD. The DCR was 81%.

Additional data showed that the median duration of response was not reached (range, 2.7-7.4+ months); the majority of responses were ongoing at the data cutoff. “There are clear responses or clear tumor regressions in those patients who had prior Topo-based ADCs with at least 1 confirmed PR,” said Ian E. Krop, MD, PhD, lead study author and associate chief in the Division of Breast Oncology at the Susan F. Smith Center for Women’s Cancers in Boston, Massachusetts, in a presentation during the conference. “However, because a full 30% of the patients on this study had a prior Topo I inhibitor-[based] ADC, and that is the same class of payload as datopotamab deruxtecan, there is a possibility of cross resistance. Therefore, we did want to look at specifically the subset of patients who had not had 1 of these prior ADCs.”

There are currently very limited standard treatments for patients with advanced or metastatic TNBC that are considered relapsed/refractory. TROP2 is highly expressed in various malignancies, including breast cancer. In the TROPION-PanTumor01 study, investigators evaluated the safety and efficacy of the TROP2-directed ADC datopotamab deruxtecan in patients with advanced or metastatic breast cancer, non-small cell lung cancer, and other tumor types.

Patients enrolled in the trial were required to have relapsed/refractory advanced or metastatic solid tumors and measurable disease per RECIST v1.1. Those with stable, treated brain metastases were permitted.

In the TNBC cohort, 42 of 44 patients received datopotamab deruxtecan intravenously (IV) at 6 mg/kg every 3 weeks, and the other 2 patients received the ADC IV at 8 mg/kg every 3 weeks. The decision to use the 6-mg/kg dose, which was selected for expansion across other tumors, as well as in the phase 3 TROPION-Lung01 (NCT04656652) and TROPION-Breast01 (NCT05104866) studies, was based on clinical results and exposure-response analyses for safety and efficacy. Additional primary endpoints were safety and tolerability; secondary endpoints included efficacy, pharmacokinetics, and anti-drug antibodies. In the TNBC cohort, the median age was 53 years (range, 32-82). The majority of patients did not have de novo metastatic disease (68%). Eleven percent of patients had brain metastases **[FIGURE]**. The median number of prior therapies in the metastatic setting was 3 (range, 1-10).
and 68% of patients had at least 2 prior lines of therapy. Previous treatments included taxanes (91%), platinum-based chemotherapy (52%), immunotherapy (43%), PARP inhibitors (16%), and Topo I inhibitor-based ADC (30%). At the data cutoff date of July 30, 2021, 31 patients (70%) discontinued treatment, including 30 due to disease progression, and 1 patient due to an adverse event (AE). Thirteen patients (30%) remained on treatment at the time of the presentation.

Furthermore, datopotamab deruxtecan showed a manageable safety profile with no new safety signals. The most frequent treatment-emergent adverse events (TEAEs) including nausea, stomatitis, vomiting, and fatigue. However, neutropenia and diarrhea were both uncommon. No cases adjudicated as treatment-related interstitial lung disease were observed.

Ninety-eight percent of patients had at least 1 TEAE, 45% of which were considered to be of grade 3 or higher; 23% experienced grade 3 or higher treatment-related TEAEs. Dose reductions due to AEs were required in 18% of patients, and 14% of patients experienced treatment interruption due to AEs. One patient discontinued treatment due to AEs, and no fatal AEs were reported.

Krop added that the hormone receptor–positive, HER2-negative cohort of TROPION-PanTumor01 is now fully enrolled and data are forthcoming. Datopotamab deruxtecan is also being explored in the phase 1b/2 BEGONIA trial (NCT03742102), which is testing the agent in combination with durvalumab (Imfinzi) as a first-line treatment for patients with metastatic TNBC. Additionally, the phase 3 TROPION-Breast01 trial is investigating datopotamab deruxtecan in hormone receptor–positive, HER2-negative breast cancer. An additional phase 3 trial of datopotamab deruxtecan in patients with TNBC is being planned, Krop said.

“We have come a long way in TNBC when we’re talking about comparing different targeted therapies, when up until a few years ago, there were no targeted therapies at all,” Krop said. “This is good progress. There is potential room for looking at this drug both in pretreated patients, like what was seen here, as well as earlier lines of therapy.”

**REFERENCES**


**TABLE. Efficacy in the TROPION-PanTumor01 Study**

<table>
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<tr>
<th>Datopotamab deruxtecan in TNBC</th>
<th>ORR</th>
<th>Confirmed CR/PR</th>
<th>Pending CR/PR</th>
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<th>PD</th>
<th>NE</th>
<th>DCR</th>
<th>Median follow-up, months (range)</th>
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<tbody>
<tr>
<td>All patients (n = 44)</td>
<td>34%</td>
<td>32%</td>
<td></td>
<td>39%</td>
<td>18%</td>
<td>5%</td>
<td>77%</td>
<td>7.6 (4-13)</td>
</tr>
</tbody>
</table>

**Patients who did not receive a Topo I inhibitor-based ADC (n = 27)**

<table>
<thead>
<tr>
<th>ORR</th>
<th>Confirmed CR/PR</th>
<th>Pending CR/PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>DCR</th>
<th>Median follow-up, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52%</td>
<td>48%</td>
<td>4%</td>
<td>33%</td>
<td>15%</td>
<td>4%</td>
<td>81%</td>
<td>8.8 (4-13)</td>
</tr>
</tbody>
</table>

ADC, antibody-drug conjugate; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

**FIGURE. Baseline Characteristics**

- **Median age, years (range):** 53 (32-82) n = 44
- **De novo metastatic disease at baseline:** Yes: 68%, No: 32%
- **Median number of prior therapies at baseline:** 3 (1-10)
- **Types of prior therapies at baseline:**
  - Taxane: 91%
  - Platinum-based chemotherapy: 52%
  - PARP inhibitors: 16%
  - Topo I inhibitor-based ADC: 30%
Have you seen the data for SARCLISA + Kyprolis® (carfilzomib) and dexamethasone?

Explore the full results of the IKEMA phase 3 trial at sarclisahcp.com
CAR Macrophage CT-0508 Shows Early Feasibility in HER2-Overexpressing Solid Tumors

by RYAN SCOTT

CT-0508, A HER2-DIRECTED CHIMERIC antigen receptor macrophage (CAR-M), has induced encouraging early results for patients with HER2-overexpressing solid tumors, according to Kim A. Reiss Binder, MD.

Reiss Binder stressed the lack of clinical implications provided by early research in the use of CAR-M. However, she pointed to promising initial safety and efficacy results from the first-in-human, multicenter, phase 1 study of adeno-virally transduced anti-HER2 CAR macrophages (NCT04660929) to suggest that CAR-M may someday have a role in treating these patients1,2 (TABLE).

“This was just a new approach to try to generate a targeted therapy using the power of macrophages directly as an anti-tumor cell, but also as a way to change the tumor microenvironment,” Reiss Binder, MD, explained. “The idea was to harness the power of macrophages and see if this could be used as a novel approach for solid tumors.”

In September 2021, the FDA granted a fast-track designation to CT-0508.

Despite progress seen with CAR T-cell products in hematologic malignancies, investigators face several roadblocks with solid tumors including the availability of natural tracking to tumors and metastatic sites, suppressive tumor microenvironments, and antigen presentation for immune activation. In immunocompetent models, investigators have demonstrated that CAR-M products overcome these barriers and has induced systemic T cell responses, modulated the tumor microenvironment, and reduced tumor size.2 CT-0508 has demonstrated improved overall survival in a preclinical model of HER2-positive cancer.2,3 Investigators are further exploring this agent in patients with recurrent or metastatic HER2-overexpressing solid tumors whose cancers do not have approved HER2-directed agents available to them or who do not respond to treatment remains ongoing. The primary outcomes of the study include safety and manufacturing feasibility through description of the percentage of products passing release criteria.2,4

Specifically, the time from growth colony stimulating factor mobilization (GM-CSF) and apheresis on days 0 and 1, respectively, to reinfusion of engineered CAR-positive macrophages is 3 weeks. The manufacturing time of CT-0508 is 1 week and includes CD14-positive monocyte selection, monocyte to macrophage differentiation using GM-CSF, followed by transduction using Ad5F35 vector encoding of a CAR transgene, and cryopreservation before delivery of the final product.2

In an interview with OncologyLive®, Reiss Binder, assistant program director of the hematology/oncology fellowship program and assistant professor of medicine at the Hospital of the University of Pennsylvania in Philadelphia, discussed the rationale behind the first-in-human study of adeno-virally transduced anti-HER2 CAR-Ms and where the research will be heading in the future.

TABLE. Key Takeaways From NCT04660929

<table>
<thead>
<tr>
<th>Category</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing</td>
<td>CT-0508 cell product was generated successfully, showing high chimeric antigen receptor expression, high viability, high purity, M1 phenotype, and good in vitro antitumor function</td>
</tr>
<tr>
<td>Safety</td>
<td>No significant treatment-related adverse events</td>
</tr>
<tr>
<td></td>
<td>No dose-limiting toxicities</td>
</tr>
<tr>
<td></td>
<td>CT-0508 infusion was well tolerated</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Short persistence of CT-0508 in the blood (approximately 4 to 6 hours)</td>
</tr>
<tr>
<td></td>
<td>consistent with rapid migration to tissue</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Serum cytokines and chemokines were only transiently increased following infusion and rapidly normalized to baseline levels</td>
</tr>
<tr>
<td>Tumor microenvironment activation</td>
<td>Single-cell transcriptomic analysis of tumor-infiltrating leukocytes demonstrated proinflammatory remodeling of the myeloid compartment and a significant enrichment and activation of tumor reactive CD8-positive T cells</td>
</tr>
<tr>
<td>Adaptive immune response</td>
<td>T-cell repertoire analysis in the blood demonstrated initiation of an adaptive immune response</td>
</tr>
</tbody>
</table>

Please explain the rationale for examining the effects of CAR macrophages on HER2-overexpressing solid tumors.

CAR T-cell therapies have been developed over several years, and at least for liquid tumors, they really changed the landscape of therapies. For solid tumors, it’s not that they won’t, but they haven’t yet gotten there.

This is just a different novel approach. The idea here was that macrophages are very present in the tumor microenvironment and have several different functions. T cells have different functions than macrophages. Not only are they cytotoxic, but they’re also antigen-presenting cells.

What was the design of the phase 1 study examining CT-0508?

This is completely a feasibility and safety study. This has never been done. These CAR-Ms have never been generated before. The number 1 priority was to make sure that it was something we could do. And then the second was to make sure that it was safe for patients to get this therapy.

The design was a single-arm, phase 1 feasibility and safety study [FIGURE]. The goal is to enroll 18 patients overall. The study population is people with advanced solid tumors who have had other standard therapies already and have had tumor progression through those therapies, and who have HER2-amplified tumors. We think of HER2-amplified tumors in breast cancer, we think of gastrointestinal cancer, but there are other tumors that are sometimes HER2 amplified. It’s almost across the board, we see [patients] with uterine cancer, ovarian cancer, cholangiocarcinoma, pancreatic cancer, colon cancer. [These] can all have HER2 amplification.

The study population is patients with any solid tumor, if they have that HER2 amplification as a tumor feature and they are progressing, meaning their tumors are growing at the time that they enter the study.

How will these novel agents be delivered to patients?

We [have] treated 3 patients at this point. The delivery method is also novel—this is part of the feasibility—can we do this? What happens is that patients first undergo Neupogen [filgrastim] to mobilize cells into the peripheral blood.
system. They then undergo an apheresis, after which those apheresis cells are sent over to the company that is generating the CAR macrophage. The monocytes they’ve collected are then matured ex vivo.

The company then matures [those monocytes] into the terminal-differentiated macrophage cells at the site, [which are then] transduced with an adenoviral vector with the HER2-targeted CAR. The cells are then processed appropriately and frozen. They are cryopreserved and shipped back to wherever the patient is across the country. [The cells] are then thawed at bedside and then infused. It’s a little bit of a lengthy process. The apheresis is not that long, but it takes a few weeks for the product to be developed.

For this trial, we allow patients to get a bridging therapy if it’s not a HER2-directed therapy. For the first 3 patients we treated, [they] were admitted to the hospital and monitored for safety. We watched them for several days to make sure they didn’t have severe [adverse] effects, and then they went home. None of the patients had a severe [adverse] effect, so moving forward, we’ll be doing this in the outpatient setting.

**Q** Expanding on the results, what are the early findings in terms of toxicity? [In the first 2 patients], we have not seen a lot in terms of toxicity. The big concern, or the thing you want to make sure you look for, is whether [patients] get cytokine release syndrome [CRS] from this product. The anticipation based on the preclinical work and the differences between macrophages and T cells was that we probably wouldn’t see severe CRS in these patients.

In the first 2 patients, 1 patient had no CRS. [On the third day], the second patient had grade 2 CRS, manifested by fever and a little bit of low blood pressure. [We] managed conservatively, and [the patient] did not require any antibody therapy or any higher level of care. It resolved quickly, within a couple of hours, and then the patient had no further symptoms.

The third patient... had no CRS either. We have not seen many concerning toxicity signals at this time; [however], we need to have a few more patients on board before we can comfortably say that this is safe.

**Q** What should be taken away from this research? What are the next steps with this modality? I want to emphasize that this study is not designed to test clinical efficacy. You always hope for clinical efficacy, but with 2 patients and a study that’s not designed to look at efficacy, I don’t know that we can say much about that. What we can say is that when we did peripheral blood draws and then, more importantly, tumor biopsies of these patients; which occur at baseline, then at the eighth day, then at week 4; we have seen changes in the tumor microenvironment [in both the first 2 patients].

We do see preliminary, early evidence that these macrophages are doing something, that the therapy is somehow changing the environment around them. We see T-cell recruitment, we see shifting toward M1 macrophages and away from tumor-resident M2 macrophages. That does not necessarily correlate or mean that there’s going to be clinical activity. But it does mean that something is happening at the site where we’re hoping something would be happening.

That is really the focus from a translational standpoint in terms of the next steps, trying to validate, build on, and figure out what that means.

From a clinical future standpoint, there’s a lot of preclinical work being done along this trial. There’s interest in combining [CAR-Ms] with PD-1 down the road and there’s interest in the future for using this modality in other ways. [Hopefully], in the next year or a couple of years, we will start to see some of those roll out.

**REFERENCES**


FOR YOUR ADULT PATIENTS WITH PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER

IF SHE RESPONDS TO CHEMOTHERAPY

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

Indication

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

Important Safety Information

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

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

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

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

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

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS1,2

OVERALL POPULATION
(N=733)

HRd POPULATION
(n=373)

Reduction in the risk of progression or death

38%

57%

REDUCTION IN THE RISK OF PROGRESSION OR DEATH

MEDIAN PFS: 13.8 MONTHS WITH ZEJULA
VS 8.2 MONTHS WITH PLACEBO
(HR, 0.62; 95% CI, 0.50-0.76) P<0.0001

MEDIAN PFS: 21.9 MONTHS WITH ZEJULA
VS 10.4 MONTHS WITH PLACEBO
(HR, 0.43; 95% CI, 0.31-0.59) P<0.0001

Study Design1,2: PRIMA, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to first-line platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

Important Safety Information (continued)

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

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

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

Please see Brief Summary on the following pages.


1L = first-line; CI = confidence interval; CR = complete response; HR = hazard ratio; HRd = homologous recombination deficient; PFS = progression-free survival; PR = partial response.

Visit ZEJULAHCP.COM to explore the PRIMA data

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Produced in USA.
1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer
ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer
ZEJULA is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies
ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
- a deleterious or suspected deleterious BRCA mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy [see Clinical Studies (14.3) of full prescribing information].

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia
Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received monotherapy with ZEJULA in clinical trials. In 1,785 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZEJULA in patients who developed secondary MDS/AML therapy-related AML varied from 0.5 months to 4.9 years. All of these patients had received previous chemotheraphy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression
Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or pancytopenia have been reported in patients treated with ZEJULA [see Adverse Reactions (6)].

In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 23%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients. In NOVA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients. In QUADRA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 28%, 27%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients.

Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy [see Clinical Study (1)]. Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following discontinuation, discontinue ZEJULA and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics [see Dosage and Administration (2.3) of full prescribing information].

5.3 Hypertension and Cardiovascular Effects
Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 321 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

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

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

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

Monitor all patients treated with ZEJULA for signs and symptoms of PFS. If PFS is suspected, promptly discontinue ZEJULA and administer appropriate treatment.

5.4 Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports [see Adverse Reactions (6.2)]. Signs and symptoms of PRES include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging.

5.5 Embryo-Fetal Toxicity
Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) of full prescribing information]. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients. Women of childbearing potential should be apprised of the potential for harm to a fetus if ZEJULA is administered during pregnancy. Therefore, ZEJULA is contraindicated in pregnant women.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception [see Warnings and Precautions (5.1) and Precautions (5.2)].

5.6 Postmarketing Experience
Data from postmarketing experience and clinical trials are limited to 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer who received ZEJULA. Serious adverse reactions in >2% of patients were nausea, vomiting, and anemia.

The most common adverse reactions in >5% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2%) each. Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (55%), and neutropenia (20%).

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

Table 1: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4a</th>
<th>Grades 3-4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=484)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plateclo (n=86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66%</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>64%</td>
<td>3%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42%</td>
<td>2%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>40%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incontinence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuromuscular and neurological disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASNALT=Asparagine transaminase/alanine aminotransferase
All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

Common Terminology Criteria for Adverse Events version 4.02.

Includes: neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.

Includes: leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.

Includes: blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatinine increased.

(continued on next page)
Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA. Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (13%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=484)</th>
<th>Placebo (n=244)</th>
<th>ZEJULA (n=484)</th>
<th>Placebo (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4</td>
<td></td>
<td></td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
<td>66</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74</td>
<td>13</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71</td>
<td>36</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>57</td>
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<td>5</td>
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<tr>
<td>Decreased neutrophils</td>
<td>66</td>
<td>25</td>
<td>23</td>
<td>1</td>
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<tr>
<td>Decreased lymphocytes</td>
<td>51</td>
<td>29</td>
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<td>3</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>46</td>
<td>21</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Increased creatinine</td>
<td>40</td>
<td>23</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Decreased magnesium</td>
<td>36</td>
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<tr>
<td>Increased aspartate aminotransferase</td>
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<tr>
<td>Increased alanine aminotransferase</td>
<td>29</td>
<td>17</td>
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</table>

Maintenance Treatment of Recurrent Ovarian Cancer

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=367)</th>
<th>Placebo (n=179)</th>
<th>ZEJULA (n=367)</th>
<th>Placebo (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4</td>
<td></td>
<td></td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>70</td>
<td>36</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>63</td>
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<tr>
<td>Increased glucose</td>
<td>63</td>
<td>56</td>
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<td>1</td>
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<td>Decreased neutrophils</td>
<td>60</td>
<td>27</td>
<td>15</td>
<td>0</td>
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<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
<td>30</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>43</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44</td>
<td>30</td>
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<td>0</td>
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<td>Increased creatinine</td>
<td>41</td>
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<td>Increased aspartate aminotransferase</td>
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<td>19</td>
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<td>0</td>
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<tr>
<td>Increased alanine aminotransferase</td>
<td>28</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

Table 6: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=367)</th>
<th>Placebo (n=179)</th>
<th>ZEJULA (n=367)</th>
<th>Placebo (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4</td>
<td></td>
<td></td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85</td>
<td>56</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72</td>
<td>21</td>
<td>35</td>
<td>0.5</td>
</tr>
<tr>
<td>Decrease in white blood cell count</td>
<td>66</td>
<td>37</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>53</td>
<td>25</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase</td>
<td>36</td>
<td>23</td>
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<td>0</td>
</tr>
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<td>2</td>
</tr>
</tbody>
</table>

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 463 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 63% of patients receiving ZEJULA. Serious adverse reactions in ≥3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA. Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in QUADRA.
6.2 Postmarketing Experience

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

Blood and lymphatic system disorders

Neutropenia includes events with preferred terms of neutropenia.

Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.

Anemia includes events with preferred terms of anemia, hemoglobin decreased, decreased albumin.

Gastrointestinal disorders

Nausea

Vomiting

Constipation

Abdominal pain

Diarrhea

General disorders and administration site conditions

Fatigue

Infections and infestations

Urinary tract infection

Investigations

Blood alkaline phosphatase increased

AST/ALT=Aspartate transaminase/alanine aminotransferase.

Musculoskeletal and connective tissue disorders

Decreased appetite

Musculoskeletal pain

Nervous system disorders

Headache

Dizziness

Psychiatric disorders

Insomnia

Renal and urinary disorders

Acute kidney injury

Respiratory, thoracic, and mediastinal disorders

Dyspnea

Cough

Vascular disorders

Hypertension

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

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</tr>
<tr>
<td>Neutropenia</td>
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<td>13</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
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<tbody>
<tr>
<td>Decreased hemoglobin</td>
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<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
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<td>40</td>
<td>4</td>
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</table>

6.6 Postmarketing Experience

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection [see Warnings and Precautions (5.1)].

Hypertension and Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first 2 months, then monthly for the first year of treatment and periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated [see Warnings and Precautions (5.2)].

Posterior Reversible Encephalopathy Syndrome

Inform patients that they are at risk of developing posterior reversible encephalopathy syndrome (PRES) that can present with signs and symptoms including seizure, headaches, altered mental status, or vision changes. Advise patients to contact their healthcare provider if they develop any of these signs or symptoms [see Warnings and Precautions (5.3)].

Dosing Instructions

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

Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

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

Pregnancy Testing

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

Contraception

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

Fertility

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

6.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily [see Dosage and Administration (2.4) of full prescribing information]. Niraparib exposure increased in patients with moderate hepatic impairment [total bilirubin ≤1.5 x upper level of normal (ULN) to 3.0 x ULN and any aspartate transaminase (AST) level]. Monitor patients for hematologic toxicity and reduce the dose further, if needed [see Dosage and Administration (2.3) of full prescribing information].

For patients with mild hepatic impairment (total bilirubin ≤1.5 x ULN and any AST level or bilirubin ≤ULN and AST>ULN), no dose adjustment is needed.

The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin >3.0 x ULN and any AST level) [see Clinical Pharmacology (12.3) of full prescribing information].

17 PATIENT COUNSELING INFORMATION

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

Methylcellulose Syndrome/Acute Myeloid Leukemia

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

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

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<th>Adverse Reaction</th>
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Blood alkaline phosphatase increased

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Musculoskeletal pain

Nervous system disorders

Headache

Dizziness

Psychiatric disorders

Insomnia

Renal and urinary disorders

Acute kidney injury

Respiratory, thoracic, and mediastinal disorders

Dyspnea

Cough

Vascular disorders

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<td>2</td>
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</table>
Amphiregulin Represents Potentially Predictive Biomarker in Acute GVHD

by LINDSAY FISCHER

AMPHIREGULIN (AREG) MAY REPRESENT a useful longitudinal monitoring biomarker for patients with life-threatening acute graft-vs-host disease (GVHD), according to sample data from 2 prospective clinical trials that were presented at the 63rd American Society of Hematology Annual Meeting and Exposition. Specifically, patients with a high baseline of AREG are at an increased mortality risk and, therefore, should be monitored consistently during serial assessments.

“Patients with life-threatening acute GVHD often have severe symptoms related to organ and tissue damage, elevated blood biomarkers of acute GVHD, or both,” lead study author Shernan Holtan, MD, of the University of Minnesota, said in a presentation of the findings. “Monitoring can be challenging [because of] unpredictable variations in symptoms that may not be related to acute GVHD severity or pathogenesis, including changes in nutrition and infections.” Holtan is an associate professor of medicine, medical director of the Masonic Cancer Center Clinical Trials Office, cochair of the GVHD Cancer Center Translational Working Group, and director of the Blood and Bone Marrow Transplant Survivorship Clinic.

Investigators evaluated AREG, ST2, and Reg3a as monitoring biomarkers in the University of Minnesota study, which treated patients with uhCG/EGF, and then compared those findings with an independent cohort of patients with steroid-refractory acute GVHD receiving second-line ruxolitinib in the REACH-1 trial (NCT02953678).

In a multivariate analysis for survival, day 28 responses (risk ratio [RR], 9.14; P < .0001) and baseline AREG (> 212 pg/mL; RR, 2.72; P < .05) were the only factors found to be independently associated with survival. When investigators evaluated these factors in a multivariate analysis in the data from the University of Minnesota study, day 28 responses (RR, 2.72; P < .05) and baseline AREG (> 212 pg/mL; RR, 4.17; P = .03) were also the only factors found to be independently associated with survival.

Samples were collected at baseline, day 7, 14, 28, and 56. The University of Minnesota study (uhCG/EGF) enrolled a total of 51 patients. AREG was measured using an enzyme-linked immunosorbent assay, and ST2 and REG3a were measured via a multiplex Luminex-based assay. In this study, there was significant positive correlations between assay platforms. The median age for first-line, high-risk patients (n = 26) in this study was 61 years (range, 22-72), there were 19 males (73%), and the number of patients with GVHD grade II, III, and IV was 2 (8%), 21 (81%), and 3 (12%), respectively.

Among the second-line cohort (n = 26), the mean age was 62 years (range, 2-69), there were 20 males (77%), and the number of patients with GVHD grade II, III, and IV was 9 (35%), 8 (31%), and 9 (35%). Severity was mostly grade 3 or 4 in both these cohorts, according to Holton.

REACH-1 enrolled 60 patients and all 3 biomarkers were assessed using microfluidic immunoassay. Among REACH-1 participants, the mean age was 52 years (range, 18-73), 31 were male (52%), and the number of patients with acute GVHD grade II, III, and IV was 22 (36.7%), 24 (40.0%), and 14 (23.3%), respectively.

In REACH-1, biomarker levels were assessed at baseline, and it was revealed that patients with day 28 progressive disease (PD) had higher baseline levels of AREG compared with patients with a day 28 complete response (CR; P < .01).

Similarly, ST2 levels were also higher for patients with day 28 PD vs CR (P < .01) or very good partial response (VGPR)/partial response (PR; P < .05).

Baseline REG3a did not adhere to the pattern; levels of this biomarker were not significantly different between patients with day 28 CR, VGPR/PR, or PD.

In the University of Minnesota study, patients with a 28-day CR experienced a 1.4-fold decrease in ST2 levels vs day 56 (P = .02). The ST2 cutoff was 188 ng/mL (P = .09), and the REG3a cutoff was 3.6 ng/mL (P = .03). “Based upon our current samples, there is not a close correlation between these biomarkers,” Holton said in a post presentation discussion. “This is the new and additional way to do monitoring.”

Holtan concluded that amphiregulin is a useful longitudinal monitoring biomarker with patients who have life-threatening acute GVHD. “We have also shown that patients with a high baseline amphiregulin are at high risk of early death,” she said. “They should be monitored on a consistent platform during serial assessments during their therapy.”

REFERENCE
Expansion of Research Is Key to Bolstering the Value of Community Oncology

by MARY CAFFREY

THE COMMUNITY ONCOLOGY SETTING offers great value and is an untapped resource for clinical trials, according to speakers from OneOncology who discussed the merits of community practice at Patient-Centered Oncology Care® (PCOC®) 2021, which took place in Nashville, Tennessee.

Duncan Allen, MHA, is senior vice president, clinical services, for OneOncology, a network of independent practices that a year ago launched OneR, a national, nonexclusive trial site management organization. Allen offered perspectives on how community oncology practices can be a resource for pharmaceutical companies that are studying increasingly rare cancers, and thus need more resources to identify patients eligible for trials.

Jeffrey Patton, MD, the CEO of OneOncology, joined the discussion and spoke to how the recent implementation of a law requiring hospitals to disclose pricing information has shed more light on distortions caused by the 340B drug pricing program. Even though community oncology practices offer greater value, Patton argued, federal policies have put community practices at a disadvantage—but he is optimistic the tide will turn.

BUILDING A RESEARCH CULTURE Patients who want to take part in oncology clinical trials would prefer to do so close to home, Allen said. Putting trials in the community has not always been easy, but the numbers point to why it is necessary: data show that with 1500 new trials per year—mostly in phase 2 as researchers dig into narrower cancer subtypes—patients that meet specific criteria are harder to find.

The focus on targeted therapies to treat rare cancers, he said, “has been a key driver to fueling this precision medicine era that we live in. [Although] that comes with a lot of excitement, I think it also comes with additional complexity that has to be tackled.”

Today, Allen said, there are more than 1000 products in late-stage development and more than 2000 in early stage. “This is an astounding statistic.” It requires practices to adapt to keep up with it all, but with this rapid change comes opportunity.

Despite the progress in the development of oncology therapeutics, he explained, the success rate of clinical trials remains very low. “This furthers the need to grow clinical trials in the community, and make sure that we’re continuing to launch therapeutic development at a rapid pace so that we can keep up with the good work that that’s coming out of the manufacturers,” Allen said.

“Community oncology, I would say, really represents the single biggest opportunity to help sponsors develop these treatments.”

Why are there not more trials in the community setting? Study selection protocols are 1 reason. Engagement by physicians is another. But as therapies become more complex, these are hurdles that must overcome, for the sake of patients. Chimeric antigen receptor (CAR) T-cell therapy, now approved in multiple blood cancers, “is a great example of having that increased operational burden,” according to Allen.

In this area, community oncology offers several “strategic advantages,” Allen said:

- ACCESS. Practices can deliver care close to home.
- DIVERSITY. Community oncology can offer a study population closer to a “real-world” experience than academia.
- SCALE. The nature of community oncology allows practices to manage study panels that are the right size for rare indications.
- INNOVATION. Allen said this “differentiator” is key—community oncology is more nimble to try new approaches in care delivery and patient experience.

Because OneR is a nonexclusive network, there are now 9 members conducting phase 2 and 3 studies in a multisided trial network. “That type of structure, we think, serves all parties well, because it creates some real skin in the game from our practices,” he said.

Key to the success has been building a research culture that focuses on recruiting scientific talent. A clinical advisory board of chief medical officers of the practices is an essential governance piece.

“From feasibility to back office functions, [such as] budgets, contracts, and regulatory [compliance], we’ve really tried to make sure our cadre of services is comprehensive in nature,” Allen said. “Lastly, we must never forget that culture eats strategy for lunch—and any research strategy must start with a nurturing culture of research at the site level.”

TRANSPARENCY REVEALS VALUE Patton followed with a talk about the “value
THE “GREAT RESIGNATION” is affecting the health care sector with ferocity, with nearly 1 in 5 health care workers having left their jobs during the COVID-19 pandemic. Many in this sector had already been experiencing varying degrees of burnout because of numerous other factors, and there was already a shortage of physicians. The pandemic made an already challenging situation worse. Since one of the primary factors contributing to physician burnout is long-term stress, it becomes more vital now for physicians to proactively address these issues.

Regardless, the end result for physicians is the same: more work and more stress. Added to this is the shortage of staff that may be creating more work for physicians as well. Being mindful of burnout and addressing it when it occurs—or, better yet, to prevent it before it occurs—is important for the same reason that the “triple aim” of the medical profession has been updated to “the quadruple aim.” The fourth aim, the health and well-being of physicians and their staffs, is necessary for achieving the other 3 aims: enhancing the patient experience, improving the health of populations, and reducing the cost of care. This has always been true, but it becomes more critical because of the pandemic and its secondary effects.

Communication and Allocation of Resources

Some ways to lessen stress are by preventing it, and one of the most important ways is to strengthen communication both internally and externally. Times like these may also warrant looking into and utilizing resources that somewhat lighten your burden. Many physicians spend unnecessary amounts of time and energy on tasks that could be done by other types of professionals—medical case managers, for instance, or members of their staff. One of these is telehealth. You can reallocate certain kinds of tasks not only lifts some of the burden from the shoulders of physicians but also can provide the additional benefit of empowering the staff.

In addition to resources that can make life easier for physicians and their staffs, there are also resources physicians can refer their patients to. One of these is telehealth. Many patients may still not realize their insurance plans offer telehealth services. Referring patients to these services can help reduce workload and ensure patients still get the care they need for medical concerns that can be adequately addressed through telehealth.

It is also worth noting that 42 states, along with the District of Columbia, require insurance providers to reimburse for telehealth. You can use the Center for Connected Health Policy’s policy finder tool for the most current regulations in your state.

Carving Out Time for Self-Care

Although it may sound obvious, in my experience, physicians need to be frequently reminded that they, too, are human. It is common for physicians to neglect their mental health. Self-care is not just a good idea; it should be considered a professional imperative. Left unaddressed, chronic stress increases the risk of not only burnout but also depression and anxiety. Physician support groups, such as the American College of Physicians Moms Group and Physician Dad Support Group on Facebook, or physician-focused support channels, such as the peer-to-peer Physician Support Line or the text-based Frontline, can help.

Digital tools such as Headspace, a leading mindfulness and stress management application, can be a useful adjunct to behavioral health services targeted toward physicians and health care providers. Normally a paid service, Headspace is offering a free 2-year subscription for American Medical Association (AMA) members throughout the pandemic.

Finally, physicians should also try to heed the same recommendations that are often given to their patients, which are basic principles, such as getting enough sleep, staying physically active, and eating as healthy as possible. Many helpful reminders such as these can be found on the AMA’s resource page for managing mental health during COVID-19. Although many of these things are certainly easier said than done, the important thing to remember is that they can indeed be done and often make all the difference.

The pandemic has opened our eyes to different ways of delivering care. With many valuable and effective resources available, it should not be about the physician doing everything. We have learned many useful lessons over the past 2 years and, hopefully, applying those lessons will help reduce burnout and increase physician resilience.

Karen Schecther, RHIA, MBA, CMPE, is a director and assistant professor in the online healthcare management and health administration programs at Maryville University in St Louis, Missouri.
Robotic Navigational Bronchoscopy Advances Diagnosis of Early-Stage Lung Cancer

by NATHANIEL IVANICK, MD, FCCP

NAVIGATIONAL BRONCHOSCOPY SEEKS TO overcome the challenges of conventional bronchoscopy, which is limited by the size and flexibility of the scope. Navigational bronchoscopy can be used during peripheral nodule biopsy for small, difficult-to-reach lung nodules that are typically not accessible using conventional bronchoscopy.

Between the windpipe and alveoli, the airways branch 17 to 24 times. Most bronchoscopes can only reach 4 or 5 of these airway divides because of the diameter of the remaining airways and limited flexibility of the scope. This results in conventional bronchoscopy being limited to the outer one-third of the lung and it carries a diagnostic accuracy of 31%. Diagnostic accuracy has increased with the application of updated ultrasound technology, such as radial endobronchial ultrasound and early navigational systems, reaching the 50% level in larger health care centers. As these ranges were still considered unacceptably low, a push for further advancements, including robotic bronchoscopy, has enhanced the diagnostic yield.

WHAT IS NAVIGATIONAL BRONCHOSCOPY?
Navigational bronchoscopy can be thought of as a global positioning system (GPS) for the bronchoscopist. Similar to a GPS device leading a driver to a distant, unfamiliar city via state highways, then down district roads and eventually city streets, a navigational bronchoscope uses a weak electromagnetic field to triangulate the positions of chest sensors, a field generator, and the scope tip to determine the biopsy location and help drive the scope to the target. Navigational bronchoscopy can be combined with virtual bronchoscopy by running a high-resolution CT scan through imaging software to “map out” the airway.

The power of robotic navigational bronchoscopy ensures increased reach, stability, and vision. The robotic scopes on the market have been demonstrated to extend an average of 4 airway branch points farther than existing ultrathin scopes. This is because of cables throughout the length of the scope that are capable of articulation, in contrast to conventional scopes which can only articulate within the last 5 cm of the scope. This articulation can be locked into place, such that a bronchoscopist can step back from the table and review slides or discuss findings without fear of the scope changing position.

The ability to lock a scope in place is a tremendous improvement over existing technologies, which can lose position during instrument insertion or as the plastic parts warmed to body temperature. Further, with the Monarch platform, for example, maintenance of scope vision out to the periphery of the lung enables the visualization of peripheral tumors before biopsy. It is therefore no surprise that the diagnostic accuracy of such procedures jumped to the mid-80% range when using navigational bronchoscopy.

“I very much look forward to new systems that will enhance both diagnostic yield and treatment effectiveness…. These treatments could be combined with other modalities, including surgery or radiation, to advance the field and improve lung cancer survival.”

— NATHANIEL IVANICK, MD, FCCP
WHO NEEDS ROBOTIC NAVIGATIONAL BRONCHOSCOPY?
We have an “epidemic” of lung nodules in the United States, with a tremendous number found each year. Between 2006 and 2012, before lung cancer screening was widely adopted, more than 1.5 million lung nodules were identified in Americans undergoing CT scans.3

Any patient with a suspicious pulmonary nodule is a candidate for robotic bronchoscopy, with the final determination dependent on the level of suspicion of lung cancer, size of the nodule, and proximity to the edge of the lung. Although robotic bronchoscopy has a slightly lower diagnostic yield than a CT-guided biopsy, it has the advantage of a slightly lower complication rate and the ability to stage the mediastinum in the same procedure.

WHAT IS THE FUTURE OF ROBOTIC NAVIGATIONAL BRONCHOSCOPY?
What new robotic navigational bronchoscopy technologies are on the horizon? I very much look forward to new systems that will enhance both diagnostic yield and treatment effectiveness. Using a robotic navigational bronchoscope and cone-beam CT, which provides a more accurate cross-sectional image directly before biopsy, interventional pulmonologists are demonstrating diagnostic yields that will rival those of CT-guided biopsies.6

Treatments that may be considered for peripheral nodules include microwave ablation, photodynamic therapy, or direct injection of chemotherapeutics into the nodules. These treatments could be combined with other modalities, including surgery or radiation, to advance the field and improve lung cancer survival.

REFERENCES

Fast Facts
Advancing Diagnosis With Navigational Bronchoscopy

- Peripheral pulmonary lesions are focal radiographic opacities typically located in the outer third of the lung which are not detectable beyond the visual segmental bronchi via flexible bronchoscopy.
- Conventional bronchoscopy has demonstrated low sensitivity for diagnosing malignant lesions with a diameter of 30 mm or less.
- Advances in navigational bronchoscopy have pushed the boundaries of evaluating peripheral pulmonary lesions.
- Techniques include: augmented fluoroscopy, cone-beam CT, and robotic bronchoscopy.

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10TH ANNUAL GIANTS OF CANCER CARE

The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

PROGRAM OVERVIEW
- Nominations are open through February 2022.
- Domestic and international nominations will be accepted.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection committee of more than 120 oncologists will vote to determine the 2022 inductees.
- The 2022 Giants of Cancer Care® class will be announced in Spring 2022.
Allison Shares His Path to Groundbreaking Achievements in Immuno-Oncology

JAMES P. ALLISON, PhD, has never hesitated to buck the system. As a teenager, the pioneering oncology investigator refused to take biology at his small-town Texas high school because the theory of evolution had been omitted from lessons for religious reasons. Instead, Allison took a university correspondence course and worked alone in an empty classroom. “I’d already decided I wanted to be either a doctor or a scientist, and I knew Darwin is to biology as Newton is to physics, so I refused to take the course. It got me into trouble with some of the teachers,” Allison said in an interview for his profile.

He went on to earn a doctorate in biological science and launch a nearly 50-year career dedicated to stimulating the human immune system to fight cancer. In November 2012, he left several leadership positions at Memorial Sloan Kettering Cancer Center, in New York, New York, to step into the chairmanship of the Department of Immunology at The University of Texas MD Anderson Cancer Center in Houston, a position he holds in addition to several others today.

Allison’s readiness to challenge the status quo has never left him. It certainly showed itself as he made discoveries about the workings of T cells, which help protect the body from pathogens. Also spurred by personal and familial experience with cancer, Allison was willing to probe his theories, even amid skepticism in the scientific community.

A case in point emerged when Allison began to suspect that the molecule CTLA-4 inhibited antibody response. He weighed that idea in the face of theories to the contrary: In textbooks, CTLA-4 had been categorized as a molecule that stimulated immune response. Allison pursued his idea anyway. The result was ipilimumab (Yervoy), which was approved by the FDA on March 25, 2011, as a treatment for unresectable or metastatic melanoma.

Allison’s years of work on that project reaffirmed his guiding philosophy. “Let your mind lead,” advised Allison, who enjoys playing blues harmonica and sailing in his free time. “Don’t pay attention to conventional wisdom if you’ve got data that show otherwise. Sometimes it’s hard to go against the system, but you have to do it if something needs to be accepted.”
Allison permanently etched his legacy into immuno-oncology with the development of ipilimumab, work that helped him win a Giants of Cancer Care® award for Scientific Advances in 2014. Four years later, the Nobel Assembly at the Karolinska Institute honored Allison and Tasuku Honjo, MD, PhD, with the Nobel Prize in Physiology or Medicine for their work that led to the use of checkpoint inhibitors in cancer treatment.

"Winning the Giants of Cancer Care® award meant a lot to me," Allison said. "For a basic scientist to be acknowledged by an award for cancer care is really fulfilling and amazing to me. For a while, I was considered an ivory-tower, pointy-headed intellectual pursuing these arcane ideas about immunology: This gives basic scientists credibility in the cancer care community."

Walking back into MD Anderson with a Nobel Prize was also a humbling experience. "One of the things I will never forget is when I came back from Stockholm and did a walk-through [of the facility] with Peter WT Pisters, MD, the president of the MD Anderson Cancer Center," Allison said in an interview with OncologyLive®, ahead of the 2021 Giants of Cancer Care® ceremony. 

"When I walked through the hospital, there were hundreds of people, patients, [and] staff just cheering. There was such an outpouring of love. I was happy to have been able to bring something back that meant so much to everyone." Allison continues to look for ways to improve the use of immunotherapy. He spoke to the direction his research has taken. "I was beginning to realize [around the time of [receiving] the Nobel Prize that, for the first time, checkpoint blockade and other immunotherapies were truly curative therapies, but the fraction of patients responding to them is relatively small at this point," Allison said. "[For example,] what we know in melanoma is that, with ipilimumab monotherapy, approximately 20% of patients are alive 10 years after a single round of treatment. This is pretty good, but why not 100%?"

"When PD-1-targeted [therapies] came along and were added to [the treatment paradigm], [survival benefit] went up to approximately 50%. That randomized trial has been out long enough now [that] there is 5 years of follow-up, and it is still at 50%. Considering that when we started this work, the median survival with melanoma was 7 months, fewer than 3% of patients were alive at 5 years, and there was no drug approved. Greater than 50% is better, but again, why not 100%?"

Allison and his scientific partner and partner in life, his wife, Padmanee Sharma, MD, PhD, a professor of genitourinary medical oncology and immunology, are working together at MD Anderson in the Immunotherapy Platform, which they developed. The platform is designed to provide support to investigators in 3 areas of development for immunotherapies: preclinical studies, immunologic monitoring for cellular and molecular analyses, and in immunopathology settings.

"I have been a basic scientist all my life and just dabbled in immunotherapy a little bit," Allison said. "Then I became a translation guy, but now we are doing reverse translation. It is clinical trial–based work, where we get specimens from patients on trials, then take them back to the laboratory and look at mechanism to try to gain insight into [possible] new combinations. We know what a good signal looks like, and we know the components of it. It is just T cells, it is myeloid cells, and we are beginning to realize that fibroblasts can play a role. It is more complicated than we thought."

For Allison, all that progress is meaningful on more than a professional level. When Allison was 10, his mother died of lymphoma. Two of her brothers also succumbed to cancers, one to melanoma and the other to lung cancer. Allison’s brother died of prostate cancer around the same time Allison underwent a prostatectomy as he fought the disease himself.

"There was a lot of urgency in the early days of ipilimumab, when we finally got the antibody made and were in the clinic," Allison said. "I was trying to hurry it along because my brother had metastatic castration-resistant prostate cancer, and I was hoping we might be able to treat him. I learned that there is only so fast you can go, and we did not get there early enough. It certainly made me appreciate doing [my] work efficiently. Speed is important, but not as important as getting it right."

Allison was in graduate school at The University of Texas at Austin when he vowed to investigate treatments for cancer. "I just thought, ‘This is a terrible thing, and there’s got to be a better way than chemotherapy and radiation,’ which my mother and one of my uncles had," Allison said. "I saw all the negative effects."

Early in his career Allison was working at the University of Texas System Cancer Center when his research sparked a discovery that has been at the heart of his work ever since: He became the first scientist to figure out how T cells recognize alien proteins within the body.

"I had been interested in immunology and T cells, which were first being recognized in the late 1960s when I was an undergraduate," Allison said. "I realized that was what I want to do as a biochemist. I wanted to work on them, but I did not have a chance until I got that faculty job [at MD Anderson]. When I came to MD Anderson, I had a project I was hired to do, but on the side, I was able to indulge my curiosity and worked out the structure of the T-cell antigen receptor for the first time in 1981." That early work saw Allison off to the University of California, Berkeley, where Allison’s 20-year stint resulted in the discovery of the costimulatory signals CD28 and CTLA-4.

In 2004, he moved again—this time to Memorial Sloan Kettering Cancer Center. There, Allison was able to analyze the immune responses of study participants to help predict which categories of patients would most likely benefit from ipilimumab, and under what circumstances. That work also helped Allison hatch ideas for second-generation drugs.

"My proudest professional moment perhaps, was being at [the American Society of Clinical Oncology (ASCO) annual meeting], when the first registration trial for ipilimumab was presented," Allison said. "That may be both personal and professional because I realized [everything had] been worth it. This [drug] is here now, and [it] is treating people, and it is going to help a lot of patients. This was a curative therapy, and it was going to change everything. I was in the middle of it, both in awe and so happy."
Watch Alex Spira, MD, PhD, FACP present data and share insights on Alunbrig® (brigatinib), a treatment option for adult patients with ALK+ mNSCLC.

**Program Objectives**

- **Share** the latest clinical efficacy and quality of life data on ALUNBRIG for ALK+ metastatic NSCLC
- **Present** a case study detailing treatment of a patient with ALUNBRIG
- **Review** important safety and dosing information
- **Enhance** your understanding of how ALUNBRIG can improve patient outcomes

**INDICATION**

ALUNBRIG® (brigatinib) is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Interstitial Lung Disease (ILD)/Pneumonitis:** Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), ILD/pneumonitis occurred in 5.1% of patients receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients. In Trial ALTA, ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred within 9 days of initiation of ALUNBRIG (median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

**Hypertension:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients. In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1, resume ALUNBRIG at the same dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

**Bradycardia:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%). In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

**Visual Disturbance:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG. In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms.

Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

**Creatine Phosphokinase (CPK) Elevation:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients. In ALTA, CPK elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3→4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation with Grade 2 or higher muscle pain or weakness. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

**Pancreatic Enzyme Elevation:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients. In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

**Hyperglycemia:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia,
ADVERSE REACTIONS

In ALTA, serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (44%), ILD/pneumonitis (37%), pyrexia (29%), dyspnea (22%), pulmonary embolism (22%), and ashenia (22%). Fatal adverse reactions occurred in 2% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA, serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90–180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90–180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90–180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) with ALUNBRIG were diarrhea (49%), fatigue (39%), nausea (39%), rash (38%), cough (37%), myalgia (34%), headache (31%), hypertension (31%), vomiting (27%), and dyspnea (26%).

DRUG INTERACTIONS

CYP3A Substrates: Avoid coadministration of ALUNBRIG with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy: ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

Lactation: There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.

Females and Males of Reproductive Potential:

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG

Contraception: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

Pediatric Use: The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

Geriatric Use: Of the 359 patients enrolled in the ALTA 1L ALUNBRIG arm and in ALTA, 26.7% were 65 and older and 7.5% were 75 and older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild or moderate hepatic impairment or mild or moderate renal impairment. Reduce the dose of ALUNBRIG for patients with severe hepatic impairment or severe renal impairment.

Please see full Prescribing Information at https://www.alunbrig.com/assets/pi.pdf
NCCN Recommends Full COVID-19 Vaccination ASAP for Most Patients With Cancer

by KYLE DOHERTY

**TABLE. General NCCN COVID-19 Vaccination Recommendations for Patients With Cancer**

<table>
<thead>
<tr>
<th>Treatment/cancer type</th>
<th>Timing to start vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT/cellular therapy</td>
<td>At least 3 months post HCT/cellular therapy</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Hematologic malignancies receiving intensive cytotoxic chemotherapy</td>
<td>Delay until ANC recovery or as soon as possible for those not expected to recover</td>
</tr>
<tr>
<td>Solid tumor malignancies</td>
<td>As soon as possible</td>
</tr>
<tr>
<td>Solid tumor malignancies undergoing major surgery</td>
<td>Separate date of surgery from vaccination by at least a few days</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; HCT, hematopoietic cell transplantation; NCCN, National Comprehensive Cancer Network.

**PATIENTS WITH CANCER SHOULD** be fully immunized against COVID-19, including third doses and/or any approved boosters, according to the most recent recommendations published by the National Comprehensive Cancer Network (NCCN) Advisory Committee on COVID-19 Vaccination and Pre-exposure Prophylaxis. 

“The medical and scientific community’s response to the COVID-19 crisis continues to be extremely encouraging, even in the face of setbacks [such as] new variants and surging infection rates,” said Robert W. Carlson, MD, CEO of the NCCN, in a press release. “Rapid research, thoughtful analyses, and tireless care delivery is allowing us to save so many more people than we could have a year ago. We hope by sharing this simplified guidance highlighting the latest research and approvals, we can help make sure the very latest in evidence-based care reaches as many patients and providers as possible.”

The committee expressed a strong preference for mRNA vaccines for patients with cancer vs adenovirus vector vaccines. The Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines are both mRNA vaccines given in a 2-dose series. The Janssen/Johnson & Johnson (Ad26.COV2.S) is an adenovirus vector vaccine given as a single dose.

Patients with solid tumor malignancies should be fully vaccinated as soon as possible, with the exception of those undergoing major surgery. Major surgery patients should separate the date of surgery from vaccination by at least a few days.

For those patients with hematologic malignancies receiving intensive cytotoxic chemotherapy, vaccination should be delayed until the absolute neutrophil count (ANC) recovery. Patients who are not expected to achieve ANC recovery and all other patients with hematologic malignancies should be vaccinated as soon as possible.

Patients undergoing hematopoietic cell transplantation (HCT) and/or cellular therapy should wait at least 3 months after the conclusion of their therapy to be vaccinated. This includes patients being treated with allogeneic transplantation, autologous transplantation, and chimeric antigen receptor (CAR) T-cell therapy.

In terms of a third dose of the mRNA vaccines, the NCCN committee supports the additional dose for patients with cancer who are immunocompromised, including those who are receiving active cancer treatment for solid tumors or cancers of the blood. For patients who received the adenovirus vector vaccine, a second dose of the same vaccine or of the mRNA vaccine should be given in place of the third dose.

A third dose is recommended for patients with solid tumor malignancies who have received cancer treatment within 1-year of initial vaccine administration. Patients with hematologic malignancies should receive an additional dose regardless of whether or not they are receiving cancer therapy, due to the fact that they are at high risk for poor serologic responses to vaccination both as a result of immunodeficiency due to the malignancy and their associated cancer therapies. The committee added that patients who have undergone treatment with HCT and/or cellular therapy should receive the third dose, with priority given to those who are less than 2 years post procedure.

The committee noted that it is important to understand the difference between a third dose for immunocompromised patients and the booster dose given to the general public. The third full dose of the mRNA vaccines is 100 μg and 30 μg for the mRNA-1273 and BNT162b2 vaccines, respectively. The dose of the booster vaccine is 50 μg for mRNA-1273 and 30 μg for BNT162b2. Among patients with a history of cancer, those who do not meet the criteria for the third vaccine dose given to immunocompromised patients should be offered a booster similar to the general population at 6 months after completion of their primary vaccine series.

Regarding the timing of the third dose, the committee agrees with the CDC that the additional dose of the mRNA vaccine should be administered at least 4 weeks after the second dose, preferably with the same vaccine that was used for the first 2 doses. The NCCN recommends a second dose for those who received the Janssen/Johnson & Johnson vaccine 2 months after the first dose with preference given to an mRNA vaccine vs a Janssen/Johnson & Johnson second dose. For patients who initially received the Janssen/Johnson & Johnson vaccine, 2 additional doses, at least 28 days apart, are recommended by the NCCN for high-risk patients and a booster at 6 months following the third dose.

When selecting patients to receive a third dose and an additional booster, the decision should be made based on the underlying cancer, therapy, and other immunocompromising conditions. The committee does not recommend the use of antibody titers to determine if patients should receive additional doses of vaccine, outside of a research study context. Patients with cancer who have a history of COVID-19 following their initial vaccine series should also receive a third dose, delayed at least 29 days post completed vaccine series and documented clearance of SARS-CoV-2 virus.

For patients who may not mount an adequate immune response to the vaccine series, the NCCN endorses the monoclonal antibody combination of tixagevimab plus cilgavimab for pre-exposure protection from COVID-19. To avoid interference with vaccine-induced immunity, tixagevimab plus cilgavimab should be administered at least 2 weeks after COVID-19 vaccination. Because of the limited supply of the combination, the committee concluded that cancer centers should prioritize distribution to patients with hematologic malignancies as these patients are more likely to have an inadequate immune response to vaccination.

REFERENCE

Making Progress Against the Blood-Brain Barrier

by JANE DE LARTIGUE, PhD

PRIMARY AND METASTATIC BRAIN tumors present a significant therapeutic challenge, in large part because they are protected by the blood-brain barrier (BBB), a highly restrictive interface between the bloodstream and the brain that prevents most drugs from accessing the brain parenchyma.1

Despite decades of research, our understanding of the BBB is still incomplete. Adding to the complexity are the changes the BBB undergoes during tumorigenesis, which are even less well understood, particularly their effect on the ability of therapeutics to access the brain.1

Nevertheless, persistent efforts by investigators and pharmaceutical companies to find ways to breach the BBB and improve the treatment of brain tumors, as well as the growing inclusion of patients with active brain metastases in clinical trials, have brought about significant advances.2-4

These include the FDA’s April 2020 approval of tucatinib (Tukysa), a HER2-targeted tyrosine kinase inhibitor (TKI), in combination with trastuzumab (Herceptin) plus capecitabine for the treatment of patients with HER2-positive breast cancer, including those with brain metastases, after prior therapy.2 Investigators said the regimen is the first to demonstrate improved activity against brain metastases in a randomized clinical trial in patients with this tumor type.6

Much of the ongoing research focuses on honing the brain-penetrating capabilities of small-molecule drugs, which are more likely to be able to pass through the BBB.5 Numerous clinical trials testing TKIs in patients with brain metastases are underway, particularly in non-small cell lung cancer (NSCLC) and breast cancer (TABLE 1).

Other strategies also are emerging. Immune checkpoint inhibitors are being evaluated in primary and metastatic brain tumors, most frequently in combination with other therapies (TABLE 2). Additionally, investigators are concentrating on finding ways to disrupt or bypass the BBB to enhance drug delivery. In a technique termed ultrasound-induced blood-brain barrier disruption (US-BBBD), the acoustic pressure from focused ultrasound (FUS) is used to excite microbubbles, which leads to transient openings in the BBB that could facilitate drug delivery. Several ultrasound devices have been developed and, following promising preclinical findings, are now in the early stages of clinical testing in cancers with brain metastases.7

ENHANCING BRAIN PENETRATION

Whether a molecule can penetrate the BBB depends on its size and physiochemical properties; nearly all large-molecule drugs and up to 98% of small-molecule drugs are thought to be unable to cross the BBB. Those that make it across the barrier may succumb to the activity of active efflux transporters that rapidly eject them.3,7

As our understanding of the BBB in the context of cancer has evolved, it has become clear that the BBB is altered by the presence of both primary and metastatic tumors in the brain. The brain-tumor barrier (BTB), as this cancer-modified BBB is known, is more permeable than the normal BBB. However, this does not appear to always work in favor of drug delivery because of the heterogeneous nature of these changes across the BTB.7

Brain metastases are the most common intracranial tumors in adults and a significant cause of morbidity and mortality. Across tumor types, metastasis to the brain occurs in an estimated 10% to 30% of patients, and its prevalence is believed to be increasing as treatments for extracranial disease become more effective.5,8

Brain metastases are particularly common in patients with lung cancer, breast cancer, renal cell carcinoma, and melanoma, with primary lung cancer accounting for approximately half of all cases.9,10

Although there have been significant advancements in the treatment paradigm for each of these cancer types in the past several decades, evidence of therapeutic efficacy against brain metastases has lagged in part because of the exclusion of patients with brain tumors from most clinical trials. This has begun to change in recent years; there was a steady decrease in the percentage of trials excluding patients with brain metastases from 2000 to 2019. The American Society of Clinical Oncology and Friends of Cancer Research have recommended that patients with treated or stable brain metastases should be routinely included in clinical trials and that those with active tumors should be considered for inclusion based on certain criteria.4

EGFR-MUTANT NSCLC

Approximately 30% of patients with EGFR-mutant NSCLC experience central nervous system (CNS) progression. The first generation of EGFR TKIs demonstrated poor activity to accumulate in the brain,1 but multiple lines of evidence suggest that the third-generation EGFR TKI osimertinib (Tagrisso) can cross the BBB and has significant activity in patients with brain metastases.11

PET imaging studies have demonstrated BBB penetration of radiolabeled osimertinib in various animal models and healthy human volunteers.12,13 Similar findings were observed in patients with T790M-mutant NSCLC in the recent ODIN-BM study (NCT03463525), in which the drug achieved rapid, high, and widespread brain exposure.12

Osimertinib is approved for the frontline treatment of metastatic NSCLC and as adjuvant therapy for earlier-stage disease after resection for patients whose tumors harbor EGFR exon 19 deletions or exon 21 L858R mutations; it also is approved as second-line therapy for metastatic NSCLC with T790M mutations.12 FLAURA (NCT02296125) and AURA3 (NCT02159198), the pivotal phase 3 trials in patients with metastatic disease, demonstrated a progression-free survival benefit in the overall cohort, as well as in subgroups of patients both with and without CNS metastases.13,14

Meanwhile, a recent analysis of results from the ADAPTAURa trial (NCT02511106), the pivotal study of osimertinib’s adjuvant indication, demonstrated that the drug cut the risk of CNS disease recurrence or death by 82% (HR, 0.18; 95% CI, 0.10-0.33), suggesting that osimertinib can protect patients against the development of CNS metastases when used in the adjuvant setting.17

Among other brain-penetrant EGFR TKIs in development, almonertinib (Ameile) is approved in China for the second-line treatment of T790M-mutant NSCLC.18 A recent study in mouse models found that almonertinib has low affinity for BBB efflux transporters and that it readily penetrates the BBB.19 The phase 1/2 APOLLO study (NCT02981108) of almonertinib in patients with EGFR T790M-mutant NSCLC who had progressed after prior EGFR TKI therapy demonstrated promising activity in patients with CNS metastases; the CNS objective response rate (ORR) was 60.9% (95% CI, 38.5%-80.3%) and median PFS was 10.8 months (95% CI, 5.5-12.6).20
ALK-POSITIVE CNS DISEASE

The first-generation ALK inhibitor crizotinib (Xalkori), which also inhibits ROS1 and MET, initially received accelerated approval for the treatment of locally advanced or metastatic ALK-positive NSCLC in 2011. Its indications have since expanded to include regular approvals for metastatic NSCLC tumors that test positive for ALK-ROS1 or for fusions. A flurry of new and more potent ALK inhibitors have since been approved to address the resistance and disease progression that frequently occur.

As with EGFR inhibitors, there has been an increasing focus on honing the ability of ALK inhibitors to cross the BBB and tackle brain metastases, which are frequently seen in patients with ALK-positive NSCLC at baseline and also have been observed at progression, including after ALK inhibitor therapy.

Although ALK inhibitors have demonstrated efficacy in patients with ALK-positive NSCLC and brain metastases, the intracranial response rate varies among agents. Some investigators hypothesize that different drug mechanisms may play a role. Crizotinib and the second-generation ALK inhibitor ceritinib (Zykadia) are substrates for the efflux transporter P-glycoprotein (P-gp), which may hinder the accumulation of drugs in the brain, although intracranial ORRs exceeding 50% have been reported in cohorts of patients treated with these agents during clinical studies.

Another second-generation ALK inhibitor, alectinib (Alecensa), which is not transported by P-gp, has been shown to accumulate in the brain in preclinical mouse models. In phase 3 trials, alectinib was found to substantially reduce the rate of progression in patients with CNS metastases compared with crizotinib. In the J-ALEX study (JapicCTI-132316), 1-year cumulative incidence rates favored alectinib over crizotinib for both CNS progression (5.9% vs 16.8%, respectively) and non-CNS progression (17.5% vs 38.4%, respectively). In ALEX (NCT02075840), CNS progression occurred in 18 patients (12%) on alectinib vs 68 patients (45%) on crizotinib (HR, 0.16; 95% CI, 0.10–0.28; P < .001). The 12-month cumulative incidence rates of CNS progression were 9.4% vs 41.4%, respectively.

Brigatinib (Alunbrig) was approved in 2020 for the frontline treatment of ALK-positive metastatic NSCLC. In final results from the phase 3 ALTA-1L trial (NCT02737501), which was the basis for the approval, brigatinib reduced the risk of intracranial progression by 56% in all patients (HR, 0.44) and by 71% in patients with any brain metastases at baseline (HR, 0.29) compared with crizotinib.

Lorlatinib (Lorbrena) is currently the only third-generation ALK inhibitor approved for the treatment of patients with ALK-positive NSCLC. It was specifically designed for enhanced BBB penetration, and imaging studies have demonstrated its rapid uptake and accumulation in the brain. In the recent CROWN trial (NCT03052608), lorlatinib was shown to elicit significantly higher intracranial response rates than crizotinib. The intracranial response rates in patients with baseline brain metastases were 82% (95% CI, 57%-96%) and 23% (95% CI, 5%-54%) in the lorlatinib and crizotinib groups, respectively.

Ensartinib (X-396) is an investigational third-generation ALK inhibitor. Recently published results from the phase 3 Exa3 trial (NCT02767804) demonstrated ensartinib’s superiority to crizotinib in patients with previously untreated ALK-positive NSCLC. Although only 11 patients with brain metastases at baseline were evaluated, the intracranial ORR was 63.6%, compared with 21.1% for crizotinib. Furthermore, significantly fewer ensartinib-treated patients went on to develop brain metastases at 12 months (4.2% vs 23.9% with crizotinib; HR, 0.32; 95% CI, 0.16-0.63; P = .001).

GAME-CHANGER TUCATINIB

Breast cancer is the second most common cause of brain metastases after lung cancer, and CNS progression is particularly frequently associated with HER2-positive disease. HER2-targeted therapies have markedly improved the prognosis of patients with this subtype of cancer.

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<table>
<thead>
<tr>
<th>Drug/manufacturer</th>
<th>Phase</th>
<th>Treatment</th>
<th>Indication</th>
<th>Trial name/ Clinicaltrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Opdivo)/Bristol Myers Squibb</td>
<td>1/2</td>
<td>+ SRS or RT +/- ipilimumab</td>
<td>NSCLC</td>
<td>NCT02696993</td>
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<tr>
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<td>2</td>
<td>Monotherapy</td>
<td>IDH1/2-mutant glioma</td>
<td>NCT03718767</td>
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<tr>
<td>Pembrolizumab (Keytruda)/Merck</td>
<td>1/2</td>
<td>+ Lenvatinib +/- quavonlimab</td>
<td>Melanoma</td>
<td>KEYMAKER-U02/NCT04700072</td>
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<td></td>
<td>1/2</td>
<td>+ SRS</td>
<td>MBC</td>
<td>NCT03449238</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>+ SRS</td>
<td>Recurrent meningioma</td>
<td>NCT04659811</td>
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<tr>
<td>Atezolizumab (Tecentriq)/Genentech</td>
<td>2</td>
<td>+ Chemotherapy</td>
<td>Extensive-stage SCLC</td>
<td>NCT04610684</td>
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<tr>
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<td></td>
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<td></td>
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</tbody>
</table>

**TABLE 1. Select Clinical Trials of Small-Molecule Inhibitors in Cancers With Brain Metastases**

<table>
<thead>
<tr>
<th>Drug/manufacturer</th>
<th>Phase</th>
<th>Treatment</th>
<th>Indication</th>
<th>Trial name/ Clinicaltrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib/AstraZeneca</td>
<td>2</td>
<td>+/- SRS</td>
<td>EGFR-mutated NSCLC</td>
<td>OUTRUN/NCT03497767 NCT03769103</td>
</tr>
<tr>
<td>Lorlatinib/Pfizer</td>
<td>2</td>
<td>Monotherapy</td>
<td>ALK/ROS1 fusion-positive NSCLC</td>
<td>NCT02927340</td>
</tr>
<tr>
<td>HER2 TKIs</td>
<td>1/2</td>
<td>+ Pembrolizumab and trastuzumab</td>
<td>HER2-positive MBC</td>
<td>TOPAZ/NCT04512261</td>
</tr>
<tr>
<td>Neratinib/Puma Biotechnology</td>
<td>2</td>
<td>+/- Capecitabine or T-DM1</td>
<td>HER2-positive MBC</td>
<td>NCT01494662</td>
</tr>
<tr>
<td>BRAF/MEK TKIs</td>
<td>2</td>
<td>+ Nivolumab</td>
<td>BRAF V600-mutant melanoma</td>
<td>NCT04511013</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)/Merck</td>
<td>1</td>
<td>+/- Binimetinib</td>
<td>BRAF V600-mutant advanced solid tumors</td>
<td>NCT04543188</td>
</tr>
<tr>
<td>CDK4/6 TKIs</td>
<td>2</td>
<td>Monotherapy</td>
<td>CDK-altered solid tumors</td>
<td>NCT02896335</td>
</tr>
<tr>
<td>Abemaciclib/Eli Lilly</td>
<td>2</td>
<td>Monotherapy</td>
<td>Meningioma</td>
<td>NCT02523014</td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>+ SRS and endocrine therapy</td>
<td>HR-positive, HER2-negative MBC</td>
<td>NCT04923542</td>
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<tr>
<td>Ribociclib/Novartis</td>
<td>1</td>
<td>Monotherapy</td>
<td>Preoperative GBM and meningioma</td>
<td>NCT02933736</td>
</tr>
</tbody>
</table>

**TABLE 2. Clinical Trials of ICIs for Brain Metastases and Primary Brain Tumors**

- **EGFR TK**
- **ALK TKIs**
- **HER2 TKIs**
- **BRAF/MEK TKIs**
- **CDK4/6 TKIs**
- **Pembrolizumab (Keytruda)/Merck**
- **Atezolizumab (Tecentriq)/Genentech**

ICIs, immune checkpoint inhibitor; MBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; SRS, stereotactic radiosurgery. TKIs, tyrosine kinase inhibitors.
MORE THAN A CENTURY AGO, renowned scientist Paul Ehrlich demonstrated that a dye injected intravenously or into the cerebrospinal fluid of animals permeated virtually all organs except the brain.¹

Underlying this observed discrepancy, we now know, was the presence of the blood-brain barrier (BBB), a term used to describe the highly specialized microvasculature-based structure that surrounds the brain parenchyma and tightly regulates the interface between the blood and the brain.¹,²

The BBB is composed of tightly packed capillary endothelial cells, which are sealed together by tight junctions to form a continuous monolayer. The endothelial cells are closely surrounded by pericytes, which mediate functions of the endothelial cells and contribute to the formation of an inner endothelial basement membrane.¹,³-⁵

A second basement membrane, the outer parenchymal membrane, is formed with assistance from a third major type of cell that populates the BBB: astrocytes. These glial cells extend cellular processes, called endfeet, which ensheath the blood vessels. In addition to playing an important role in BBB formation, the astrocytes provide a signaling connection between the blood vessels and neuronal circuitry (FIGURE).²-⁵

The BBB serves as a physical, metabolic, and immunologic barrier to the brain and plays a vital role in maintaining brain homeostasis by providing protection from toxic substances, removing waste products, and facilitating the supply of essential nutrients, ions, and hormones.¹,⁵,⁶

Small gaseous molecules, such as oxygen and carbon dioxide, and some small (< 500 Da) lipophilic molecules can passively diffuse across the lipid membrane surrounding the endothelial cells.⁶ Nonetheless, free movement across the BBB is largely restricted. Molecular traffic that would pass paracellularly through the gaps between adjacent endothelial cells elsewhere in the body is forced by the BBB’s tight junctions to take a transcellular route. This involves a vesicle capturing the molecular cargo on the luminal (blood) side of the endothelial cell, traversing the cell, and ejecting the cargo on the opposite, abluminal (brain) side.⁶

The BBB is lined with transport proteins and receptors that act as sentries, regulating transport across the BBB via various routes, depending on the type of molecule to be transported. Essential nutrients, such as glucose and amino acids, are transported by carrier-mediated transcytosis. Certain positively charged macromolecules can pass across the BBB using the nonspecific adsorptive-mediated transcytosis, whereas more specific and selective uptake is facilitated by receptor-mediated transcytosis.⁶ Efflux transporters, predominantly members of the adenosine triphosphate-binding cassette superfamily such as P-glycoprotein, are also highly involved in transporting molecules out of the BBB.

Some components of the blood-brain barrier (BBB) undergo changes during the course of a malignancy, shifting the BBB to the blood-tumor barrier (BTB) and prompting alterations in the brain around the tumor (BAT) region. Illustration courtesy of Daniel Hertzberg/Purdue University.
Investigators have thought that HER2-targeted antibody-drug conjugates (ADCs) were too large to cross the BBB. However, this concept may be challenged by the novel ADC fam-trastuzumab deruxtecan-nxki (Enhertu), which demonstrated a promising intracranial response rate of 83.3% (of 5 patients) in preliminary results from the phase 2 TUXEDO-1 trial (NCT04752059). Several small-molecule HER2 inhibitors with varying degrees of brain penetration are on the market. Most recently approved is the third-generation drug tucatinib. Tucatinib has not been directly shown to cross the BBB, but physiologically based pharmacokinetic modeling has predicted that it will be able to penetrate both the BTB and BBB and achieve pharmacologically active concentrations.

Approval of tucatinib was largely based on results from the phase 2 HER2CLIMB trial (NCT02614794), in which the agent was combined with trastuzumab (Herceptin) and capecitabine for patients with previously treated metastatic HER2-positive breast cancer. Participants with brain metastases made up 48% of the cohort, and both this subgroup and the overall population displayed significantly higher 1-year PFS rates among patients who received the tucatinib combination compared with placebo plus trastuzumab and capecitabine.

The FDA approval includes patients with brain metastases, making tucatinib the first targeted therapy specifically approved in this patient population. In a follow-up report, the tucatinib combination was also found to improve overall survival (OS)—the first drug to achieve this feat in HER2-positive patients with brain metastases—reducing the risk of death by 42% (HR, 0.58; 95% CI, 0.40–0.85; P = 0.005).

BBB DISRUPTION

Although significant advancements have been made in the development of small molecules that cross the BBB, the fact remains that almost all drugs, including monoclonal antibodies and most chemotherapy agents, are unable to penetrate the protective barrier without assistance. Numerous strategies have been tested to bypass the BBB, including convection-enhanced delivery, which uses a pressure gradient to facilitate direct delivery of the drug into the target tissue; intranasal delivery, which is thought to allow drug access to the brain through the olfactory and trigeminal neural pathways; and intra-arterial drug delivery, which involves administration of the drug directly into an artery in the proximity of the tumor. These methods have had limited success treating brain tumors to date, but clinical trials are ongoing.

There have also been significant efforts to penetrate the BBB via transcytosis by encapsulating drugs in nanoparticles or conjugating them to ligands that trigger receptor-mediated uptake. A notable example of the latter approach is ANG1005, which consists of angiopep-2, a peptide that recognizes the LRPI receptor on the surface of brain endothelial cells, conjugated to paclitaxel.

In a phase 2 trial of ANG1005 in patients with breast cancer and brain metastases, a subset with leptomeningeal carcinomatosis (n = 28) had prolonged OS compared with historical controls. The ongoing phase 3 ANGLeD study (NCT03613181) is evaluating ANG1005 in patients with HER2-negative breast cancer who have newly diagnosed leptomeningeal carcinomatosis and previously treated brain metastases.

Physical disruption of the BBB to temporarily increase its permeability is another strategy that is gaining in popularity. Several methods have been tested, but the use of FUS coupled with intravenously administered microbubbles, or US-BBBD, has shown the most promise.

The acoustic pressure from the ultrasound causes the microbubbles to expand and contract, placing mechanical stress on the endothelial cells of the BBB and temporarily opening tight junctions between these cells, creating gaps through which drugs may pass in a process termed paracellular transport. The integrity of the BBB is typically fully restored within 24 hours after disruption.

A major obstacle to delivering ultrasound to the brain is the thickness of the skull; the resulting ultrasound distortion necessitates the use of MRI or neuronavigation for safe guidance of the device. At least 3 specialized systems are in development for US-BBBD in the brain. ExAblate and NaviFUS are extracranial devices; the former consists of a hemispherical ultrasound helmet containing over 1000 transducers coupled with a magnetic resonance scanner, and the latter is a frameless navigation-guided device. The SonoCloud system has an implantable ultrasound emitter, which is activated by a transcutaneous needle. Extracranial FUS can be radiologically guided by concurrent MRI or navigation.

US-BBBD has had significant success in preclinical studies, demonstrating the ability to safely, effectively, and transiently open the BBB to enhance the penetration of various drugs, thus improving antitumor efficacy.

Early-phase clinical trials have begun, and promising preliminary data are emerging for both MRI- and neuronavigation-guided US-BBBD in patients with primary brain tumors and brain metastases. For example, in a first-in-human trial in 4 patients with HER2-positive breast cancer with brain metastases (NCT03714243), MRI-guided FUS safely enhanced the delivery of trastuzumab to the brain.

REFERENCES

For your adult patients living with Lambert-Eaton myasthenic syndrome (LEMS),

IT’S TIME FOR A COMEBACK

Help your adult patients move forward with FIRDAPSE® (amifampridine), the only FDA-approved, evidence-based therapy for the treatment of LEMS in adults.

FIRDAPSE has been proven in clinical trials to significantly improve muscle strength and patient perception of well-being.¹

INDICATIONS AND USAGE:

FIRDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

SELECTED IMPORTANT SAFETY INFORMATION

FIRDAPSE can cause seizures. Do not use FIRDAPSE in patients with a history of seizures, or with a hypersensitivity to amifampridine or another aminopyridine.

Please see Brief Summary of full Prescribing Information on the next page.

Reference: ¹. Full Prescribing Information for FIRDAPSE (amifampridine), Catalyst Pharma; 2021.

Visit www.FIRDAPSEHCP.com to learn more.
FIRDAPSE® (amifampridine) tablets for oral use 

INDICATIONS AND USAGE 
FIRDAPSE® is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

DOSAGE AND ADMINISTRATION 
The recommended starting dosage is 15 mg to 30 mg daily taken in divided doses (3 to 4 times daily) during the open-label phase of Study 1. The starting dosage is expected to be increased in 5 mg daily every 3 to 4 days.

If the maximum dosage of 80 mg daily cannot be tolerated, dosage may be reduced. Consider discontinuation or dose reduction of FIRDAPSE® in patients who have a seizure while on treatment.

FIRDAPSE® is contraindicated in patients with:
- A history of seizures
- Hypersensitivity to amifampridine phosphate or any other anionpore

WARNINGS AND PRECAUTIONS 

SEIZURES 
FIRDAPSE® can cause seizures. Seizures have been observed in patients without a history of seizures taking FIRDAPSE® at the recommended doses, at various times after initiation of treatment, at an incidence of approximately 2%. Many of the patients were taking medications that had contraindicated medical conditions that may have lowered the seizure threshold. Seizures may be dose-dependent. Consider discontinuation or dose-reduction of FIRDAPSE® in patients who have a seizure while on treatment. FIRDAPSE® is contraindicated in patients with a history of seizures.

Hypersensitivity 
In clinical trials, hypersensitivity reactions and anaphylaxis associated with FIRDAPSE® administration have not been reported. Anaphylaxis has been reported in patients taking another anionpore, therefore, it may occur with FIRDAPSE® if anaphylaxis occurs. Administration of FIRDAPSE® should be discontinued and appropriate therapy initiated.

ADVERSE REACTIONS 
The following serious adverse reactions are described elsewhere in the labeling:
- Seizures
- Hypersensitivity

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 the rates observed in clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials (Study 1 and 2) in patients with LEMS, 83 patients were treated with FIRDAPSE®, including 40 patients treated for more than 6 months, and 35 patients treated for more than 12 months. In an uncontrolled access program, 115 patients with LEMS were treated with FIRDAPSE®, including 102 patients treated for more than 6 months, 77 patients treated for more than 12 months, and 53 patients treated for more than 18 months. Study 1 was a double-blind, placebo-controlled, randomized discontinuation study in adults with LEMS. Following an initial open-label run-in phase (up to 81 days), patients were randomized to either continue FIRDAPSE® treatment or transition to placebo for a 16-day double-blind phase. Following final assessments, patients were allowed to resume FIRDAPSE® treatment for up to 2 years (open-label, long-term safety phase of the study).

During the open-label run-in phase of Study 1, 53 patients received FIRDAPSE® for an average of 38 days at an average daily dosage of 50.5 mg/day. The average patient age was 52.3 years and 66% were female. There were 52 patients who had no prior exposure to FIRDAPSE® at the initiation of this study. Table 1 shows adverse reactions with an incidence of 5% or greater occurring in ≥2 LEMS patients newly initiated on treatment with FIRDAPSE® in the run-in phase of the study.

Table 1. Adverse Reactions in ≥5% of LEMS Patients Newly Treated with FIRDAPSE® in Study 1

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<thead>
<tr>
<th>Adverse Reaction</th>
<th>N=53</th>
<th>(%)</th>
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</thead>
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<tr>
<td>Muscle cramps</td>
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<td>62.3</td>
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<tr>
<td>Upper respiratory tract inflammation</td>
<td>33</td>
<td>62.3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>33</td>
<td>62.3</td>
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<tr>
<td>Pain in extremity</td>
<td>28</td>
<td>52.8</td>
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<tr>
<td>Gait disturbance</td>
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<td>Constipation</td>
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<td>Diarrhea</td>
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<td>17.0</td>
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<tr>
<td>Pain in rectum</td>
<td>7</td>
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</table>

ADVERSE REACTIONS 
The incidence of adverse reactions (N=42) during the double-blind phase of Study 1 (10/09/01) including the double-blind phase and the 2-year open-label long-term study phase, additional adverse reactions occurring in at least 3% of the patients included: dyspnea, urinary tract infection, gastritis/gastritis, flushing, insomnia, peripheral edema, paresthesia, myalgia, myalgia/paresthesia, pyrexia, viral infection, blood creatine phosphokinase increase, dermatitis, lymphoma/lymphoid neoplasia, urticaria, and increased liver enzymes. These patients received an average daily dosage of 66 mg of FIRDAPSE®.

DRUG INTERACTIONS 
Doses of LEMS drugs with cholinergic effects should be significantly decreased or discontinued in patients receiving FIRDAPSE® to decrease risk of adverse reactions.

Table 2. Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Amphotericin B</td>
<td>Amphotericin B</td>
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</tr>
<tr>
<td>Azathioprine</td>
<td>Azathioprine</td>
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</tr>
<tr>
<td>Cimetidine</td>
<td>Cimetidine</td>
<td>Significant decrease or discontinuation</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Ciclosporin</td>
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<tr>
<td>Cyclosporin</td>
<td>Cyclosporin</td>
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<td>Diltiazem</td>
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<tr>
<td>Disopyramide</td>
<td>Disopyramide</td>
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<tr>
<td>Dronabinol</td>
<td>Dronabinol</td>
<td>Significant decrease or discontinuation</td>
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<td>Fluoxetine</td>
<td>Fluoxetine</td>
<td>Significant decrease or discontinuation</td>
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<tr>
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<td>Imipramine</td>
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<tr>
<td>Lidocaine</td>
<td>Lidocaine</td>
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<tr>
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<td>Lithium</td>
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<td>Ketoconazole</td>
<td>Ketoconazole</td>
<td>Significant decrease or discontinuation</td>
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<td>Omeprazole</td>
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<tr>
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<td>Opioids</td>
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<tr>
<td>Quinidine</td>
<td>Quinidine</td>
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<td>Tacrolimus</td>
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<td>Tolbutamide</td>
<td>Tolbutamide</td>
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</tr>
<tr>
<td>Verapamil</td>
<td>Verapamil</td>
<td>Significant decrease or discontinuation</td>
</tr>
</tbody>
</table>

Other Adverse Reactions 
In the overall population treated in Study 1 (n=53), including the double-blind phase and the 2-year open-label phase, an additional 8% (N=4) experienced adverse reactions that were classified as serious. These included: psychogenic polydipsia, paresthesias, facial edema, and pruritus vulvae. Other reported adverse reactions that were not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS 

FIRDAPSE® tablets are not to exceed a maximum of 80 mg daily. In the overall population treated in Study 1 (n=53), including the double-blind phase and the 2-year open-label phase, an additional 8% (N=4) experienced adverse reactions that were classified as serious. These included: psychogenic polydipsia, paresthesias, facial edema, and pruritus vulvae. Other reported adverse reactions that were not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Cervical Cancer Treatment Paradigm Is Bolstered With Newly Approved Therapies

TREATMENT OF PATIENTS WITH metastatic cervical cancer remains challenging—the 5-year overall survival (OS) rate is just 17%.1 Whereas many other solid tumors have seen a plethora of FDA approvals of clinically meaningful treatments, there has been a paucity of new approvals for metastatic cervical cancer. However, the tide began to turn in 2021 with several new treatments receiving FDA approval and showing a meaningful incremental benefit over previously available agents.

During a recent OncLive Peer Exchange®, a panel of experts in gynecologic cancer shared their insights on the treatment landscape for metastatic cervical cancer in the first- and second-line settings, including data for the newly approved agents and considerations for using them in clinical practice. They also discussed several promising checkpoint inhibitors on the horizon. “It’s exciting to see this flurry of activity in cervical cancer. We have tripled the survival rate, which is heartwarming and incredible for our patients. This field is going to continue to evolve,” Bhavana Pothuri, MD, said.

First-Line Metastatic Cervical Cancer Treatment

Managing metastatic cervical cancer in the first-line setting includes treating women with de novo stage IVB or recurrent cancer after chemotherapy or radiation, Bradley Monk, MD, FACOG, FACS, said. “We don’t count chemotherapy or radiation as a line of therapy,” he said.

In patients with metastatic cervical cancer, the standard chemotherapy backbone remains paclitaxel (Taxol) and platinum, either cisplatin or carboplatin. “We were originally using a cisplatin backbone and the JGOG [Japanese Gynecologic Oncology Group] trial demonstrated noninferiority between carboplatin and cisplatin, except for those [patients] who had not received cisplatin previously as a part of their RT [radiation therapy] planning,” Warner K. Huh, MD, FACOG, FACS, said.

The panelists proceeded to discuss 2 practice-changing, phase 3 clinical trials that have assessed additions to the standard-of-care chemotherapy backbone of paclitaxel plus platinum in the first-line setting: the Gynecologic Oncology Group GOG 240 trial (NCT00803062), which investigated the addition of bevacizumab (Avastin), and KEYNOTE-826 (NCT03635567), which investigated the addition of pembrolizumab (Keytruda).

GOG 240

In 2014, the FDA approved bevacizumab in combination with standard-of-care chemotherapy based on data from the GOG 240 trial,
making it the first drug approved for patients with late-stage cervical cancer since the 2006 approval of topotecan with cisplatin.\(^2\)\(^,\)\(^3\)\[^{[GOG 240]}\] showed that by incorporating antiangiogenesis therapy into platinum and nonplatinum chemotherapy doublets we could significantly improve survival in women with recurrent metastatic cervical cancer in the first line,\(^4\)\(^,\)\(^5\) Krishnansu S. Tewari, MD, said.

The study randomly assigned 452 women with persistent, recurrent, or late-stage cervical cancer to receive paclitaxel and cisplatin with or without bevacizumab, or paclitaxel and topotecan with or without bevacizumab. In those receiving the triplet, OS reached 16.8 months, whereas those receiving chemotherapy alone had an OS of 12.9 months, showing a 3.9-month OS benefit with the addition of bevacizumab. Extended follow-up showed the benefit of incorporating bevacizumab to be sustained, with an OS of 16.8 months with the triplet and 13.3 months with the chemotherapy doublets, demonstrating a 3.5-month OS benefit with the addition of bevacizumab (HR, 0.77 95% CI, 0.62-0.95; \(P = .007\)).\(^6\)

Although there is a small OS benefit with the addition of bevacizumab to standard-of-care chemotherapy, the panelists indicated that not all patients are candidates for this treatment. “There are contraindications, [including] fistula, GI [gastrointestinal] perforation, nonhealing wounds, proteinuria, uncontrolled hypertension, inflammatory bowel disease, [and] a history of diverticulitis,” Monk said.

Despite such contraindications, the panelists indicated that many of their patients are treated with the triplet. “Approximately 85% of my patients will get the triplet,” Pothuri said, noting she is thoughtful about counseling her patients on the benefits and drawbacks of treatment with bevacizumab.

**KEYNOTE-826**

On October 13, 2021, just a few weeks after the *Onclive Peer Exchange*, pembrolizumab received FDA approval in combination with chemotherapy with or without bevacizumab for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 with a combined positive score (CPS) of at least 1, as determined by an FDA-approved test. This marked the first new first-line therapy approval for women with persistent, recurrent, or metastatic cervical cancer since bevacizumab’s approval in 2014. FDA approval of pembrolizumab was based on data from KEYNOTE-826, which showed improvements in the dual primary end point of progression-free survival (PFS) and OS with the addition of pembrolizumab to standard-of-care chemotherapy.

Investigators of KEYNOTE-826 randomly assigned 617 women with persistent, recurrent, or metastatic cervical cancer in a 1:1 ratio to receive pembrolizumab 200 mg (n = 308) or placebo (n = 309) every 3 weeks for up to 35 cycles plus standard-of-care chemotherapy, with bevacizumab administered per investigator discretion.\(^7\) Of these patients, 548 had a PD-L1 CPS of at least 1 (273 in the pembrolizumab arm and 275 in the placebo arm) and 317 patients had a CPS of at least 10 (158 in the pembrolizumab arm and 159 in the placebo arm).

In the first protocol-specified interim analysis, among the 548 women with a PD-L1 CPS of at least 1, the median PFS was 10.4 months in the pembrolizumab arm and 8.2 months in the placebo arm. “That was a hazard ratio of 0.62, which is incredible. We have these results within the first 3 months, and you see those curves diverge,” Premal H. Thaker, MD, MS, said. A median PFS of 10.4 months was also observed when considering the 317 patients with a PD-L1 CPS of at least 10 (HR, 0.58; 95% CI, 0.44-0.77; \(P < .001\)) as well as the entire intention-to-treat population (N = 617; HR, 0.65; 95% CI, 0.53-0.79; \(P < .001\)).

“The OS hasn’t been accomplished yet,” Thaker said. Nevertheless, estimates of patients alive at 24 months significantly favor pembrolizumab versus placebo across all patient subgroups examined (*TABLE 1*).

TABLE 1. 24-Month Estimate of Patients Alive in the KEYNOTE-826 Trial by Subgroup\(^8\)

<table>
<thead>
<tr>
<th>PD-L1 CPS ≥ 1</th>
<th>Intention-to-treat</th>
<th>PD-L1 CPS ≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>Placebo</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Patients alive, %</td>
<td>53.0%</td>
<td>50.4%</td>
</tr>
<tr>
<td>HR for death (95% CI)</td>
<td>0.64 (0.50-0.81)</td>
<td>0.67 (0.54-0.84)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

CPS, combined positive score.

Thaker said that no unexpected adverse effects (AEs) were observed in the study. The most common grade 3 to 5 AEs included anemia, affecting 30.3% of patients in the pembrolizumab arm versus 26.9% in the placebo arm, and neutropenia, affecting 12.4% of patients in the pembrolizumab arm versus 9.7% in the placebo arm.\(^9\) A little more than 60% of patients in both the pembrolizumab and placebo arms received bevacizumab in addition to standard-of-care chemotherapy. “What I can’t tease out from the data is if you need bevacizumab for the pembrolizumab to work,” Tewari said, who was a study investigator and coauthor of the *New England Journal of Medicine* article outlining the interim results.\(^5\) Although the data are challenging to interpret, the panelists agreed that clinicians should continue to use bevacizumab when they deem it appropriate for their patients. “Pembrolizumab shouldn’t confuse that decision,” Monk said.

Additionally, Thaker emphasized that pembrolizumab is a good option to have because patients who are not candidates for bevacizumab can still benefit. “You can use it to your advantage for your patient; that was the take-home [message]. If you have a patient with diverticulitis or proteinuria and you feel you can’t [use bevacizumab], there’s a benefit for these patients [with pembrolizumab],” she said.

**SECOND-LINE METASTATIC CERVICAL CANCER TREATMENT**

Despite the recent advancement in treating patients with metastatic cervical cancer in the first-line setting, most patients progress and require second-line treatment.

**TABLE 2. NCCN Recommended Second-Line or Subsequent Therapy for Metastatic Cervical Cancer**

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Pembrolizumab (PD-L1–positive or MSI-H/dMMR tumors)*</th>
<th>Nivolumab (PD-L1–positive tumors)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other recommended regimens</td>
<td>Albumin-bound paclitaxel*</td>
<td>Bevacizumab*</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil*</td>
<td>Gemcitabine*</td>
</tr>
<tr>
<td></td>
<td>Irinotecan*</td>
<td>Mitomycin*</td>
</tr>
<tr>
<td></td>
<td>Topotecan*</td>
<td>Vinorelbine*</td>
</tr>
<tr>
<td></td>
<td>Tisotumab vedotin-ts*</td>
<td></td>
</tr>
</tbody>
</table>

**Useful in certain circumstances**

| Pembrolizumab (TMB-H tumors)* | Larotrectinib or entrectinib (NTRK gene fusion–positive tumors)* |

*Category 2A recommendation

*Category 2B recommendation
Although there are many second-line options available (TABLE 2), response and OS rates associated with these agents have been “fairly minimal,” Huh said. The panelists explained that response rates have ranged from 0% to 10% with physician’s choice of chemotherapy to 14.3% with pembrolizumab, demonstrating a great unmet need in this area.

Since response with available treatments is so low, Huh said he tries to put his patients on clinical trials whenever possible. Tewari agreed with this approach. “The space has blown up with trials, so fortunately most of our patients in need of second-line therapy in the last few years were able to secure a place on a study,” he said.

The panelists noted that numerous promising agents are currently in clinical trials, with one such agent, tisotumab vedotin (Tivdak), recently approved by the FDA.7 The panelists said that the approval of tisotumab vedotin is particularly exciting because it has shown unprecedented response rates, reaching almost 25%.

Tisotumab Vedotin

On September 20, 2021, tisotumab vedotin was granted FDA accelerated approval for women with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.7

“Is the first antibody-drug conjugate [ADC] to get approved in a gynecologic malignancy,” Monk said. He explained that this agent “has a target, an antibody, a linker, and a cytotoxin” and that its promising efficacy may result from its multiple mechanisms of action, including monomethyl auristatin E–directed cytotoxicity and bystander immunogenic effects.

Tisotumab vedotin received an accelerated approval from the FDA based on data from the phase 2, open-label, multicenter, single-arm innovaTV 204/GOG-3023/ENGOT-cx6 trial (NCT03438396).4 In the study, 101 women with recurrent or metastatic previously treated cervical cancer (ie, squamous cell, adenosquamous, or adenocarcinoma treated with no more than 2 previous systemic regimens for recurrent or metastatic disease) received at least 1 dose of tisotumab vedotin. After a median follow-up of 10 months, the confirmed objective response rate (ORR) was 24% (95% CI, 16%-33%), with 7 patients (7%) achieving complete responses and 17 patients (17%) achieving partial responses (TABLE 3).

“It’s game-changing….I have several patients who are excited to go on this drug,” Huh said. Other panelists reported similar sentiments among their patients because of the paucity of meaningful treatments, particularly for those who are PD-L1 negative and do not qualify for immune checkpoint inhibitors. Monk recounted the emotional response of one of his patients when he informed her of her biopsy results, tisotumab vedotin’s approval, and that it was a viable option for her. “This is an opportunity,” he said. Tewari agreed and said he is thrilled this agent has been approved because he has already seen some “phenomenal objective responses” in some of the study patients he treated.

Tisotumab vedotin was found to have a manageable toxicity profile. The most common AEs included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (26%), and dry eye (23%). Treatment-related AEs grade 3 or higher were reported in 28% of patients and included neutropenia (3%), fatigue (2%), ulcerative keratitis (2%), and peripheral neuropathies (2%). Serious treatment-related AEs occurred in 13% of patients, with peripheral sensorimotor neuropathy (2%) and pyrexia (2%) being the most common. There were 4 deaths, 3 of which were deemed unrelated to treatment and 1 attributed to septic shock from treatment.

Tisotumab vedotin has been found to cause changes to the corneal epithelium and conjunctiva. Its prescribing information has a boxed warning regarding its ocular toxicity.9 “It’s the linker that’s causing the ocular toxicity. It’s not the payload or the antibody,” Tewari said, noting that the mitigation strategies required by the

<table>
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<tr>
<th>Outcome</th>
<th>Tisotumab vedotin (N = 101)</th>
</tr>
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<tbody>
<tr>
<td>CR (%)</td>
<td>24% (15.9%-33.3%)</td>
</tr>
<tr>
<td>PR (%)</td>
<td>7%</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>8.3 (4.2-NR)</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; ORR, overall response rate; NR, not reached; PR, partial response.

FDA are highly effective in reducing the risk of ocular AEs, particularly severe AEs that can result in permanent vision loss. An ophthalmic exam is required at baseline, before each infusion, and as clinically indicated. Additionally, 3 types of eye drops are required throughout tisotumab vedotin treatment: vasoconstriction eye drops immediately before the infusion, topical corticosteroid eye drops for 72 hours after the infusion, and topical lubricating drops for the duration of treatment and up to 30 days after the final infusion.

Monk said when ocular AEs occur, they tend to happen early in treatment and are completely reversible. “You have to emphasize that,” he said, noting that eye concerns can be unsettling for patients. “For conjunctivitis, it’s primarily red eye. I’ve seen patients who have someone ask, ‘What’s wrong with your eye? Is that pink eye? Is that contagious?’ It’s disturbing, but it’s not serious,” he explained.

The panelists noted that dealing with intensive ocular care requirements can pose challenges for oncologists and patients, especially if patients need to see an ophthalmologist before every cycle, but they explained that such situations are not
new for oncologists. “When I first started using this drug, I was scared and apprehensive, but now that I’ve seen the mitigation strategy I understand it, similarly to how we were scared with BEV [bevacizumab]. I remember learning about anti-hypertensives, and asking how many can we give? What would we give? But we’ve gotten better, and we will continue to improve,” Thaker said.

CHECKPOINT INHIBITORS ON THE HORIZON

The panelists noted that several new immune checkpoint inhibitors are being investigated for patients with metastatic cervical cancer, including balstilimab and cemiplimab (Libtayo). Balstilimab was under consideration as a monotherapy for this indication, but its biologic license application (BLA) was voluntarily withdrawn in October 2021 following FDA approval of pembroli-zumab, which came 4 months earlier than the FDA goal date.10 Despite this setback, development of this agent is moving forward but as part of a combination therapy for metastatic cervical cancer and other tumor types.

One partner for the anti-PD-L1 antibody balstilimab that has shown promise is zalifrelimab, a CTLA-4 antibody. In a phase 2 trial (NCT03495882), after a median follow-up of 21 months, the confirmed ORR with the combination was 25.6% (95% CI, 18.8%-33.9%), which included 10 complete responses and 22 partial responses.11 In patients with PD-L1-positive tumors, the ORR reached 32.8%, whereas it was 9.1% in PD-L1-negative tumors. Although responses were observed across histologic subtypes, the ORR was highest for patients with squamous tumors, reaching 32.6% (vs 8.8% of cervical adenocar-cinomas). The overall disease control rate was 52% (95% CI, 43.3%-60.6%). Hypothyroidism (14.2%) and hyperthyroidism (7.1%) were the most common immune-mediated AEs.

“The response rate with the combination appears to be superior to single-agent [balstilimab],” Pothuri said. She surmised that “the addition of the CTLA-4 may help overcome the lack of efficacy with a single-agent checkpoint inhibitor” and suggested this combination may receive wide adoption if approved.

Similar to balstilimab, cemiplimab is a PD-L1 inhibitor. It was accepted for priority review in September 2021 as a treatment for patients with recurrent or metastatic cervical cancer whose disease progressed on or after chemotherapy.12 The supplemental BLA was submitted to the FDA based on data from the phase 3, open-label, multicenter EMPower-Cervical 1 trial (NCT03257267), which showed significant benefit with cemiplimab vs chemotherapy in global health status/quality of life, physical functioning, and key symptom scales.13 Importantly, cemiplimab also was associated with a survival benefit.14

“We showed a significant improvement in overall survival in the squamous cell population, which was the first part of our statistical hierarchy, 11 vs 8 months. We also showed a significant improvement in survival in the intention-to-treat population [12.0 vs 8.5 months]. Although it wasn’t planned or part of the statistical hierarchy, the results with adenocarcinoma were thought-provoking [13.3 vs 7.0 months]. It was a tolerable monotherapy. We didn’t have to combine it with bevacizumab or chemotherapy. Going forward, this is an important option for patients,” Tewari said. The target action date for the FDA’s decision is January 30, 2022.15 A key feature of the trial is that patients were enrolled regardless of PD-L1 expression status, which may help extend checkpoint inhibitors to all-comers if ultimately approved.

In their concluding thoughts, the panelists expressed significant excitement for the future, noting that treatment development for patients with metastatic cervical cancer is only the tip of the iceberg but is progressing at a rapid pace. “In 2 years, I think the algorithm for how we treat patients with recurrent cervical cancer will be completely different. It’s the dawn of a new era. It’s incredibly exciting,” Huh said.

REFERENCES


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ARE YOU THINKING DEEP ENOUGH
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Relapse is expected,
but deep response could be too\textsuperscript{1,2}

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

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