COVID-19 Spurs New Therapy Trends

PEER EXCHANGE
Clinical Factors Drive Choice of CDK4/6 Inhibitor Therapy in BREAST CANCER

WORLD CONFERENCE ON LUNG CANCER
New Strategies for Resectable NSCLC Are Among the Highlights

OncPathways®
Ki-67 May Play Larger Role as a Breast Cancer BIOMARKER

CLINICAL PERSPECTIVES
Targeted Strategies in GI CANCERS Top ASCO’s List of Advances

JOHN THEURER CANCER CENTER
JTCC and Georgetown’s Research Alliance Achieves New Level With IMMUNOTHERAPY Breakthrough
For adults with intermediate- or high-risk myelofibrosis (MF)\(^1\)

**INTERVENE WITH**

**JAKAFI\(^\circledR\) (RUXOLITINIB) AT DIAGNOSIS**

Ruxolitinib (Jakafi) is a Category 2A* treatment option for both symptomatic lower-risk\(^1\) and higher-risk MF – in patients with platelets $\geq 50 \times 10^9$/L.\(^{2,3}\)

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.\(^{2}\)

Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate risk based on MIPSS-70 (threshold of $\leq 3$ prognostic variable points), and very low, low, or intermediate risk based on MIPSS-70+ (version 2.0; threshold of $\leq 3$ prognostic variable points).\(^{2}\)

In patients who are not transplant candidates.

**SIGNIFICANTLY MORE PATIENTS RECEIVING JAKAFI EXPERIENCED IMPROVEMENT IN MF-RELATED SPLENOMEGALY\(^1,3,5\)**

**COMFORT-I PRIMARY ENDPOINT\(^{1,3,5}\)**

42% of patients receiving Jakafi achieved a $\geq 35\%$ reduction in spleen volume at week 24

VS

0.7% of patients receiving placebo ($P < 0.0001$)

4.4 years median duration of spleen response among primary responders ($n = 65$)\(^{4,3}\)

**COMFORT-II PRIMARY ENDPOINT\(^{1,5,11}\)**

29% of patients receiving Jakafi achieved a $\geq 35\%$ reduction in spleen volume at week 48

VS

0% of patients receiving best available therapy\(^1\) ($P < 0.0001$)

Indications and Usage

Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

Important Safety Information

- Treatment with Jakafi\(^\circledR\) (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $< 0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi. Platelet transfusions may be necessary
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt

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

Please see Brief Summary of Full Prescribing Information.
JAKAFI 3-YEAR AND 5-YEAR OVERALL SURVIVAL ANALYSES

COMFORT-I: 5-YEAR ANALYSIS OF JAKAFI AND PLACEBO
- At 3 years, survival probability was 70% for patients originally randomized to JAKAFI and 61% for those originally randomized to placebo.
- Overall survival was a prespecified secondary endpoint in COMFORT-I.

JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 51%
- All patients in the placebo group either crossed over to JAKAFI at a median of 9 months or discontinued.
- The 5-year overall survival analysis is not included in the Full Prescribing Information for JAKAFI. Although the 3-year overall survival analysis is presented in the Full Prescribing Information, P values and hazard ratios are omitted from the overall survival Kaplan-Meier curves.

COMFORT-II: 5-YEAR ANALYSIS OF JAKAFI AND BEST AVAILABLE THERAPY
- At 3 years, survival probability was 79% for patients originally randomized to JAKAFI and 59% for those originally randomized to best available therapy.
- Overall survival was a prespecified secondary endpoint in COMFORT-II.

JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 56%
- All patients in the best available therapy group either crossed over to JAKAFI at a median of 17 months or discontinued.
- BAT, best available therapy.

For more data on long-term results with JAKAFI, visit JAKAFIResults.com.

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

To learn more about JAKAFI, visit HCP.JAKAFI.com.

References:

JAKAFI and the JAKAFI logo are registered trademarks of Incyte. All trademarks are the property of their respective owners. © 2020, Incyte Corporation. MAT-JAK-02211 07/20

or discontinue JAKAFI without consulting their physician. When discontinuing or interrupting JAKAFI for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.

- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.

- Treatment with JAKAFI has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating JAKAFI. Monitor and treat according to clinical guidelines for hyperlipidemia.

- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥50%) were infections.

- Dose modifications may be required when administering JAKAFI with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.

- Use of JAKAFI during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking JAKAFI should not breastfeed during treatment and for 2 weeks after the final dose.

Overall Survival Kaplan-Meier Curves by Treatment Group in COMFORT-I

Overall Survival Kaplan-Meier Curves by Treatment Group in COMFORT-II

Adapted with permission from Leukemia.

Adapted with permission from the Journal of Hematology & Oncology.

For data on long-term results with JAKAFI, visit JAKAFIResults.com.
ANKETCALTIN: For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE
Myelofibrosis: Jakafi is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. Post-polycythemia Vera Jakafi is indicated for treatment of polycythemia vera (PV) in patients with an inappropriate red blood cell mass.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Thrombocytopenia, Anemia and Neutropenia: Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Dosage and Administration (2.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2.1), and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Perform a treatment completion blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2.1), and Adverse Reactions (6.1) in Full Prescribing Information].

Risk of Infection
Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. Tuberculosis Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. Progressive Multifocal Leukoencephalopathy Progression of multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [see Adverse Reactions (6.1) in Full Prescribing Information].

Hematopoietic Dysfunction Jakafi may cause hematopoietic dysfunction [see Adverse Reactions (6.1) in Full Prescribing Information]. Patients with esterase are not used as monitoring parameters in patients with CKD.

Hematology Laboratory Abnormalities
Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Jakafi (N=151)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>19 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Anemia</td>
<td>96 %</td>
<td>34 %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 %</td>
<td>1 %</td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline.

National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-Controlled Study
25% of patients with Jakafi and 1% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was 2% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Clinical Trial Experience in Polycythemia Vera Jakafi was evaluated in a single-arm, dose-escalation study in patients with polycythemia vera. The study was a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see Clinical Trials (7.4) in Full Prescribing Information].

The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in <1% of patients treated with Jakafi and <1% of patients treated with placebo.

Table 3 provides the most frequent nonhematologic adverse reactions occurring up to Week 12.

Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥5% of Patients on Jakafi in the Open-Label, Active-Controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>15 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>6 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

Table 3 continued.
Table 3 continued.

Table 3:  Myelofibrosis: Worst Hematology Laboratory Parameter All Grades (%) Grade 3-4 (%) Grade 3-4 (%) Grade 3-4 (%) Jakafi (N=110) Best Available Therapy (N=111)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>72 &lt;1 &lt;1</td>
<td>58 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 5 &lt;1</td>
<td>24 3 &lt;1</td>
<td>10 &lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 0 &lt;1</td>
<td>10 &lt;1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinical Trial Experience in Acute Graft-Versus-Host Disease

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

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

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

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

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>75 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chemistry

Elevated ALT          | 48 8            |             |             |
Elevated AST          | 48 6            |             |             |
Hypertiglyceridemia   | 11 1            |             |             |

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
* Includes dizziness and vertigo
* Includes dyspepsia and rashes
* Includes herpes zoster and post-hepatic necrosis
* Includes weight increased and abnormal weight gain
* Includes urinary tract infection and cystitis

Selected laboratory abnormalities during treatment with Jakafi are shown in Table 6.
The coronavirus disease 2019 (COVID-19) pandemic not only forced changes in the mechanics of delivering oncology care but also in clinical protocols. Some changes in radiation schedules, the administration of oral therapies, and new combinatorial approaches may become standards of care after the danger from COVID-19 fades.

From the Editor
Optimism Plays a Vital Role in Outcomes for Patients With Cancer
By Maurie Markman, MD

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It’s Time to Focus on the Future

WHEN CORONAVIRUS DISEASE 2019 (COVID-19) began to grip the United States last year, the oncology community quickly recognized the disruptive impact that the pandemic would have on cancer care. Telehealth visits were embraced, office procedures were altered, and clinical protocols were reviewed.

Now, a year after former President Donald Trump declared COVID-19 a national emergency, the toll the pandemic has taken in missed screenings, diagnoses, and postponed care is becoming apparent. For example, investigators who analyzed claims in a Medicare database found sharp declines in numerous services, including screenings, biopsies, surgeries, and chemotherapy administration, from March through July 2020 compared with the same period in 2019. April 2020 was the cruelest month; for example, biopsies declined 79% for colon, 71% for breast, and 58% for lung procedures compared with April 2019.

Confronted with the difficulties of treating patients during a pandemic, the oncology community has proved to be resourceful and creative in adjusting protocols. The cover story in this issue of OncologyLive® reports several changes in radiotherapy, drug administration, and supportive care that might be viewed as advances as time goes on. We also feature updated information on practice resources and recent data about COVID-19 and cancer care.

Certainly, it is time to start looking to the future of oncology care, particularly with 3 FDA-authorized vaccines becoming increasingly available to the public and the extensive advances made in treating COVID-19.

“When the pandemic first hit the United States, a short delay in care was an appropriate choice for many cancer types,” Robert W. Carlson, MD, CEO of the National Comprehensive Cancer Network, said in a recent press release. “However, the balance of risk has shifted significantly. Postponing cancer care will add tragedy on top of tragedy.”

We heartily agree. As we move forward, our content team at OncLive.com is focused on helping to shape the future through up-to-date information and expert insights.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES

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Get the latest breaking news, specialty coverage, and conference coverage sent straight to your inbox.
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®. 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 24% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jiroveci pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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

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

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

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

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

INDICATIONS

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

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

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

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%), diarrhea (41%), anemia (38%), neutropenia (35%), musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%). The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%), thrombocytopenia (16%), and pneumonia (14%).

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

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%). The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 28% of patients.

Confidence built on 150,000+ patients treated worldwide†

†Across all indications as of September 2019.

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

DRUG INTERACTIONS

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

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see brief summary on the following pages.
IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA treatment and follow dose modification guidelines

Light-headedness, syncope, chest pain) or new onset dyspnea. Manage cardiac ECG for patients who develop arrhythmic symptoms (e.g., palpitations, Periodically monitor patients clinically for cardiac arrhythmias. Obtain an

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14</td>
<td>8*</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Purpura</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>
† Includes one event with a fatal outcome.

IMBRUVICA® (ibrutinib)

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements and adverse reactions

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

<table>
<thead>
<tr>
<th>Body Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>41</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

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

* One patient death due to histiocytic sarcoma.

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

<table>
<thead>
<tr>
<th>Body Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>24</td>
</tr>
</tbody>
</table>
The body system and individual ADR terms are sorted in descending frequency order for each ADR term.

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

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

Table 8: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

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

* Includes multiple ADR terms

† Includes 1 event of hemorrhagic cyst with fatal outcome in each arm, and 1 event of pneumonia with fatal outcome in the ofatumumab arm.

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

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

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

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

Table 8: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

**iLLUMINATE**: Adverse reactions described below reflect exposure to IMBRUVICA with a median duration of 11.7 months in patients treated with IMBRUVICA + BR and 9.6 months in patients treated with placebo + BR.

**Adverse reactions leading to discontinuation** were atrial fibrillation, congestive heart failure, fluid retention, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>Ibrutinib + BR (N=287)</th>
<th>Placebo + BR (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Bruising*</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Bruising*</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**Table 10: 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 Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain*</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Body System</td>
<td>Adverse Reaction</td>
<td>IMBRUVICA + R (N=75)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising*</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Rash*</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

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

* Includes multiple ADR terms.

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

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

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

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

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + R (N=75)</th>
<th>Placebo + R (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising*</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>Rash*</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

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

| Body System Adverse Reaction | IMBRUVICA + R (N=75) | Placebo + R (N=75) | |
|------------------------------|----------------------|-------------------| |
| Gastrointestinal disorders   |                      |                   | |
| Diarrhea                     | 43                   | 5                 | |
| Nausea                       | 25                   | 0                 | |
| Dyspepsia                    | 19                   | 0                 | |
| Stomatitis*                  | 17                   | 2                 | |
| Abdominal pain               | 16                   | 2                 | |
| Constipation                 | 14                   | 0                 | |
| Abdominal pain upper         | 13                   | 0                 | |
| Vomiting                     | 11                   | 2                 | |
| General disorders and administrative site conditions |         |                   | |
| Fatigue                      | 44                   | 6                 | |
| Peripheral edema             | 24                   | 2                 | |
| Pyrexia                      | 17                   | 2                 | |
| Skin and subcutaneous tissue disorders |        |                   | |
| Bruising*                    | 41                   | 0                 | |
| Rash*                        | 29                   | 5                 | |
| Pruritus                     | 14                   | 0                 | |
| Musculoskeletal and connective tissue disorders |         |                   | |
| Musculoskeletal pain*        | 40                   | 3                 | |
| Arthralgia                   | 24                   | 2                 | |
| Muscle spasms               | 19                   | 3                 | |
| Infections and infestations  |                      |                   | |
| Upper respiratory tract infection |          |                   | |
| Sinusitis*                   | 21                   | 0                 | |
| Bronchitis                   | 19                   | 0                 | |
| Pneumonia*                   | 11                   | 10                | |

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

* Includes multiple ADR terms.

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

Table 15: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + R (N=75)</th>
<th>Placebo + R (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
The body system and individual ADR preferred terms are sorted in descending frequency order.

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

Table 15: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

<table>
<thead>
<tr>
<th>Percent of Patients (N=63)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (3%) and neutropenia (6%) occurred in patients.

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Table 16 and Table 17 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 16: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD in Study 1121 (N=42)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypoalbuminemia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hemorrhage</td>
<td>30</td>
<td>2†</td>
</tr>
<tr>
<td></td>
<td>Hypertension*</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

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

* Includes multiple ADR terms.
† Includes 2 events with a fatal outcome.
Females and Males of Reproductive Potential:

Maternal Condition.

Along with the mother's clinical need for IMBRUVICA and any potential effects on milk production.

The development and health benefits of breastfeeding should be considered.

Ibrutinib or its metabolites in human milk, the effects on the breastfed child,

Effect of CYP3A Inducers on Ibrutinib:
The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.4) in Full Prescribing Information]. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.4) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

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

Use in Specific Populations:

Pregnancy:

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

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

Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL and major vessels) and increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily, respectively.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential:

Contraception:

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

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

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 2 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.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information].

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

Patient Counseling Information:

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

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

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

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

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

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

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

• Embryo-fetal toxicity: Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA [see Warnings and Precautions].

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

• Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.6) in Full Prescribing Information].

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

• Advise patients to inform their healthcare 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

Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent http://www.imbruvica.com

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© Janssen Biotech, Inc. 2019

PRC-06112
THESE ARE CLEARLY CHALLENGING TIMES.
The current political climate in our country, the soaring number of deaths resulting from the coronavirus disease 2019 (COVID-19) pandemic, the ongoing struggle with the COVID-19 vaccine rollout, and the intensity of anti-vaccine rhetoric are among the negative developments that unfortunately may serve as the focus of our thoughts and discussions.

For individuals with cancer, the pandemic has brought additional challenges: substantial delays in obtaining recommended screenings, medical attention for worrisome signs or symptoms (eg, new onset of a persistent cough in a smoker), or care for an established diagnosis—all while grappling with concerns about the safety of in-person appointments and essential therapeutic interventions. To this list one must add the rather poorly defined risks potentially associated with developing a COVID-19 infection during or following active therapy, as well as anxiety about the ever-escalating costs associated with medical care and existing and future anti-neoplastic agents.

But rather than focus on these important, concerning aspects of the cancer journey, this commentary highlights how individuals respond to these and multiple other challenges that patients with cancer may have to confront. Let’s focus on optimism, a topic that is fraught with as much controversy as any in the oncology arena.

Consider, for example, reports over the last decade in the peer-reviewed medical literature suggesting that a majority of patients with advanced metastatic cancer do not appear to acknowledge that currently available therapy cannot cure their malignancy. These reports imply that the patients’ oncologists either inappropriately or inadequately convey information or that patients are unable to understand the facts regarding outcomes.\(^1\)\(^2\) Apparently, some analysts view as inappropriate a patient’s refusal to allow this terrible diagnosis of cancer to prevent them from maintaining an optimistic perspective.

In his landmark and stunningly effective essay, “The Median Isn’t the Message,” the eminent evolutionary biologist, the late Stephen Jay Gould, PhD, had this perspective on the survival curve for abdominal mesothelioma after being diagnosed with the malignancy and given only a few months to live: “The distribution was, indeed, strongly right skewed, with a long tail (however small) that extended for several years above the 8-month median. I saw no reason why I shouldn’t be in that small tail, and I breathed a very long sign of relief.”\(^3\)

Is such an optimistic focus harmful? Remarkably, to some, the answer appears to be yes. In one commentary, the author directly challenges the assertion of Dr Gould, declaring: “If patients focus only on the tail of the survival curve to become exceptional responders, then by definition the overwhelming majority will be unprepared for their fate. Thus viewed, ‘the median isn’t the message’ is dangerous.”\(^4\) So much for a patient with cancer attempting to maintain an optimistic perspective despite a catastrophic diagnosis. So much for the value of the human spirit and faith.

**BENEFITS OF FAITH AND POSITIVE THINKING**
Although more should surely be said in strong opposition to this view, it is important to focus on peer-reviewed articles that provide increasingly robust support for the relevance of optimism and faith in the face of serious medical conditions, including cancer.

In a population-based study, investigators who followed more than 74,000 individuals for 16 years found a lower mortality rate among women who attended weekly religious services vs those who never attended services; the research team suggested that “participation may enhance
From the Editor

the social integration that promotes healthy (eg, tobacco-free) behaviors and provides social support, optimism, or purpose. Findings from a meta-analysis of 15 cohort studies involving 229,391 participants revealed that an objectively measured optimistic vs pessimistic perspective after a cardiovascular event was significantly associated with a reduced risk of a subsequent cardiovascular event (relative risk [RR], 0.65; P < .001) and all-cause mortality (RR, 0.86; P < .001).

In the cancer arena, strong evidence exists for the impact of distressing or destabilizing life events to negatively affect relevant outcomes. A population-based study in Sweden revealed a striking increase in suicide during the first week and first year following a diagnosis of malignancy, particularly when a poor prognosis was predicted. Similarly, a large population-based report using the Surveillance, Epidemiology, and End Results Program database found that recent divorce, likely representing a major disruption in an individual’s life, is associated with inferior cancer outcomes.

Evolving data provide provocative support for the relevance of an optimistic vs a pessimistic perspective in influencing outcomes in serious malignant conditions. Investigators from the Mayo Clinic examined survival outcomes in 534 patients with lung cancer who had completed a personality assessment 18 years prior to their diagnosis; a nonpessimistic explanatory style was associated with a 6-month improvement in overall survival. And, in a report involving interviews with 26 long-term survivors of ovarian cancer (23 with advanced disease), investigators noted that these individuals “had a strong life purpose, which manifested as positivity, taking charge of their lives and advocating for themselves.”

Clearly, this commentary has only barely scratched the surface regarding the potential for optimism to favorably influence a patient’s cancer journey, but hopefully these observations will generate meaningful discussion and debate.

REFERENCES

FDA DIGEST

Liso-cel Gets Green Light for Large B-cell Lymphomas

The FDA has approved the CD19-directed chimeric antigen receptor (CAR) T-cell product isocabtagene maraleucel (liso-cel; Breyanzi) for the treatment of adult patients with certain types of large B-cell lymphoma who have not responded to, or who have relapsed after, at least 2 other types of systemic treatment. Specifically, the indication includes patients with diffuse large B-cell lymphoma not otherwise specified, including that which arises from indolent lymphoma; high-grade B-cell lymphoma; primary mediastinal large B-cell lymphoma; and follicular lymphoma grade 3B.

The application was based on data from the phase 1 TRANSCEND-NHL-001 trial (NCT02631044) in which 192 patients were evaluated after receiving liso-cel in the intended dose range of 50 to 110 × 10^6 CAR-positive viable T cells. Findings from the trial showed an objective response rate of 73% (95% CI, 67%-80%), a complete response (CR) rate of 54% (95% CI, 47%-61%), and a partial response rate of 19% (95% CI, 14%-26%), with time to first CR or partial response occurring at a median of 1 month.

Overall, 114 patients had a response, the median duration of which was 16.7 months (95% CI, 5.3-not reached). Of the 104 patients who achieved CR, 68 (65%) had a remission lasting at least 6 months and 64 (62%) had a remission lasting 9 months.


Umbralisib Is Approved for Multiple Lymphoma Types

The FDA has granted an accelerated approval to umbralisib (Ukonqi) for the treatment of patients with relapsed/refractory marginal zone lymphoma (MZL) who have previously received at least 1 anti-CD20-based regimen and patients with relapsed/refractory follicular lymphoma who have received at least 3 prior lines of systemic therapy.

The approval of the PI3Kδ and CK-1-e inhibitor was based on findings from the phase 2b UTX-TGR-205 trial (NCT02793583). The first cohort evaluated included 69 patients with MZL; findings showed that the agent elicited an overall response rate of 49.0% (95% CI, 37.0%-61.6%), including a complete response rate of 16%. The median duration of response had not yet been reached (95% CI, 9.3-not evaluable) in this cohort.

For patients with follicular lymphoma (n = 117), the overall response rate was 43% (95% CI, 33.6%-52.2%) with 3% of patients achieving a complete response. The median duration of response was 11.1 months (95% CI, 8.3-16.4).

TO READ MORE, VISIT https://bit.ly/2MSwnTQ.

Cemiplimab-rwlc Receives Go-ahead for 2 Advanced BCC Indications

Cemiplimab-rwlc (Libtayo) has been granted regular approval by the FDA for the treatment of patients with locally advanced basal cell carcinoma (BCC) that has previously been treated with a Hedgehog pathway inhibitor (HHI) or for whom an HHI is not appropriate. The agency also granted accelerated approval to cemiplimab for the treatment of patients with metastatic BCC previously treated with an HHI or for whom an HHI is not appropriate.

The approvals of the PD-1–directed monoclonal antibody were based on findings from the pivotal phase 2 Study 1620 (NCT03132636), which examined patients with unresectable locally advanced BCC or metastatic BCC (nodal or distant). Investigators reported that among 84 patients with local advanced BCC, the confirmed objective response rate was 29% (95% CI, 19%-40%) and the median duration of response was not reached (range, 2.1-17.4+ months). Further, 79% of responders maintained their response for at least 6 months.

Among 28 patients with metastatic BCC, the confirmed objective response rate was 21% (95% CI, 8%-41%), the median duration of response was not reached (range, 9.2-25.0+ months), and all responders maintained their responses for at least 6 months.

Continued approval of the metastatic BCC indication may be contingent upon verification and description of clinical benefit.


GUIDELINE UPDATE

ASCO Issues New Adjuvant Therapy Guidelines in Breast Cancer

The American Society of Clinical Oncology (ASCO) has released updated guidelines concerning the selection of optimal adjuvant chemotherapy and targeted therapy for patients with early breast cancer, a review that was prompted by data for ado-trastuzumab emtansine (T-DM1; Kadcyla) and the availability of biosimilars.

ASCO’s multidisciplinary group of experts addressed 2 clinical questions: Should adjuvant T-DM1 be administered after completion of standard preoperative chemotherapy and HER2-targeted therapy in all patients with HER2-positive breast cancer with residual invasive cancer in the breast or lymph nodes at surgery? Among patients with HER2-positive breast cancer who receive adjuvant trastuzumab therapy, do trastuzumab (Herceptin), trastuzumab and hyaluronidase-oysk (Herceptin Hyllecta), and currently available FDA-approved biosimilars of trastuzumab differ regarding safety or efficacy?

The update was based on a review of findings from the phase 3 KATHERINE trial (NCT01772472), in which patients with HER2-positive early breast cancer and residual disease after neoadjuvant chemotherapy were treated with either adjuvant T-DM1 (n = 743) or trastuzumab (n = 743). The trial data showed that T-DM1 reduced the risk of invasive disease by 50% over trastuzumab (HR, 0.50; 95% CI, 0.39-0.64; P < .001). Moreover, the findings demonstrated patients who received T-DM1 had a significant improvement in invasive disease-free survival at 3 years compared with those who received trastuzumab, 88.3% and 77.0%, respectively (95% CI, 0.39-0.64; P < .0001).

Regarding the first clinical question, ASCO concluded that, “Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity.” In terms of the second clinical question, ASCO said, “Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars.”

REFERENCE


Vol. 22 | No. 05 | MARCH 2021
Drug Spotlight

Trastuzumab Deruxtecan Enters Treatment Paradigm for Gastrointestinal Cancer Subtypes

by JASON HARRIS

FAM-TRASTUZUMAB DERUXTECAN-NXXI (ENHERTU)
represents a potential new standard of care for adults with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

The FDA approved the new indication for the HER2-directed antibody-drug conjugate (ADC) on January 15, 2021, for patients who previously received trastuzumab (Herceptin)-based therapy. The agency initially approved the drug in December 2019 for patients with previously treated unresectable or metastatic HER2-positive breast cancer.

The latest indication is based on findings from the phase 2 DESTINY-Gastric01 trial (NCT03329690). The data demonstrated that treatment with trastuzumab deruxtecan resulted in an improvement in median overall survival compared with physician’s choice of irinotecan or paclitaxel, at 12.5 vs 8.4 months, respectively (HR, 0.59; 95% CI, 0.39–0.88; P = .0097).1

The ADC also elicited a higher confirmed objective response rate versus chemotherapy. In the 126 patients who received trastuzumab deruxtecan, the response rate was 40.5% compared with 11.3% in the 62 patients who received chemotherapy (P<.0001).

Notably, the indication includes a boxed warning for embryo-fetal harm and interstitial lung disease (ILD)/pneumonitis. Physicians are advised to look for cough, dyspnea, fever, and other respiratory symptoms.

In an interview with OncologyLive®, Yelena Y. Janjigian, MD, chief of the Gastrointestinal Medical Oncology Service at Memorial Sloan Kettering Cancer Center in New York, New York, talked about what the approval of trastuzumab deruxtecan means for patients with this disease and the importance of reaffirming the presence of HER2 throughout therapy.

What was noteworthy about the patient response to this drug?
In the main cohort of the study, all patients were HER2 positive; the HER2 low-expressing cohort was presented separately. A study in the New England Journal of Medicine1 looked at patients who were HER2 immunohistochemistry [IHC] 3+ or IHC 2+ based on archival samples, not samples taken at the most recent progression. What was remarkable about the study is that, despite having a heavily pretreated patient population in the third-line setting, the overall response is clinically meaningful and has not been previously demonstrated by any HER2-directed agents in later lines of therapy.

Could trastuzumab deruxtecan become the new standard of care in patients with previously treated gastric or GEJ cancers?
It’s important to note that the DESTINY-Gastric01 study focused on patients in later lines—third line or beyond. Despite that, the FDA approved use of trastuzumab deruxtecan after progression of disease on trastuzumab; in other words, potentially in the second-line setting, third line, and beyond. What also is interesting to note is that the FDA label does suggest and encourage biopsies at the time of progression. That’s very important to note because 20% to 30% of tumors lose HER2 overexpression after progression on a trastuzumab-based therapy.

Therefore, if you’re going to go after HER2 as a target, it would be important to confirm that it is still present in the tumor.

Studies are underway to evaluate and understand how this drug could be used in the first-line setting and its potential in that setting. Right now in first-line settings, we’re focused on combinations with anti-PD-1–based therapies; regimens [include] pembrolizumab [Keytruda] plus trastuzumab in combination with first-line fluoropyrimidine oxaliplatin–based therapy, which is being explored in the phase 3 setting in the KEYNOTE-811 trial (NCT03615326).

Can you describe the mechanism of action for this drug?
Trastuzumab deruxtecan is an antibody-drug conjugate that uses a trastuzumab-based inhibition with a crosslinking agent and a chemotherapy payload that is quite potent. The cytotoxic ratio to targeted agent ratio is higher than other ADCs that were studied before, such as TDM-1 [ado-trastuzumab emtansine; Kadcyla]. Here, trastuzumab deruxtecan uses 8 chemotherapy payload molecules to a HER2-directed molecule. The agent that’s being used is the topoisomerase inhibitor DM1. It’s really a potent agent, and it is active in gastrointestinal malignancies, particularly in gastric cancer.

In terms of safety, how does trastuzumab deruxtecan compare with existing therapies?
This drug is typically well tolerated. Adverse effects related to cytotoxic chemotherapy, such as decreased white blood cell count and gastrointestinal toxicity, could be seen. One adverse effect that’s important to note and to be aware of is ILD, which is an effect related to HER2 inhibition and HER2 binding in normal epithelial cells and lung interstitial cells. That’s something to be on the lookout for, particularly since in the breast cancer studies and colorectal cancer studies treatment-related deaths were reported from ILD.

In gastric cancer, there were no treatment-related deaths reported thus far, and with close monitoring, dose interruptions, and dose reductions, the patients did well.

ILD is something to monitor your patients for, both radiographically and clinically.

What is next in the treatment of HER2-positive gastric cancers?
Trastuzumab deruxtecan has shown efficacy in [this] disease. It’s important to build on that efficacy and continue to try to understand which patients need to continue on HER2 inhibition and which patients need to be changed to other types of therapy because of loss of HER2.

I would encourage biopsies in the second-line setting to confirm that the target is present before switching therapy. Use of next-generation sequencing, as well as liquid biopsies or circulating tumor DNA, has helped us understand the heterogeneity of HER2 expression and gastric and esophageal cancer. We need to continue to test our patients for HER2 standard [therapy] in the first-line setting and retest again in second line.

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

For a full list of references, see the article at Oncelive.com.
PIVOTAL CLINICAL TRIAL
DESTINY-Gastric01 (NCT03329690) is a phase 2, randomized, open-label, multicenter study of 188 patients with HER2-positive advanced gastric cancer who had progressed after receiving at least 2 prior therapies, including trastuzumab. Patients were randomized 2:1 to receive either trastuzumab deruxtecan 6.4 mg/kg every 3 weeks or physician's choice of chemotherapy (irinotecan or paclitaxel).

BASELINE PATIENT CHARACTERISTICS:
Median age, years (range)
65 (34-82)
66 (28-82)

Primary site
Stomach 86%
Gastroesophageal junction 14%

Histological subtype
Intestinal 71%
Diffuse 22%
Other 6%

HER2 expression
IHC 3+ 77%
IHC 2+ or ISH-positive 24%

REFERENCE

Mechanism of action:
- Trastuzumab deruxtecan is composed of a humanized anti-HER2 antibody, IgG1, and the small molecule DXd, a topoisomerase I inhibitor attached by a cleavable linker. After binding to HER2 on tumor cells, trastuzumab deruxtecan undergoes internalization and intracellular linker cleavage by lysosomal enzymes.

How supplied:
- 100-mg lyophilized powder in a single-dose vial

Dosing:
- 6.4 mg/kg given as an intravenous (IV) infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity
  - Do not administer as an IV push or bolus.
  - Do not use sodium chloride injection.

Company: Daiichi Sankyo, Inc

EFFICACY RESULTS IN THE DESTINY-GASTRIC01 TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab deruxtecan (n = 126)*</th>
<th>Physician’s choice chemotherapy (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>12.5 (9.6-14.3) HR, 0.59; 95% CI, 0.39-0.88; P = .0097</td>
<td>8.4 (6.9-10.7)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.6 (4.3-6.9) HR, 0.47; 95% CI, 0.31-0.71</td>
<td>3.5 (2.0-4.3)</td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>40.5% (31.8%-49.6%) P &lt; .0001</td>
<td>11.3% (4.7%-21.9%)</td>
</tr>
<tr>
<td>CR</td>
<td>7.9%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>32.5%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>11.3 (5.6-NR)</td>
<td>3.9 (3.0-4.9)</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

a The efficacy population includes 1 patient who enrolled on the study but was not treated.

Boxed warnings
- Interstitial lung disease/pneumonitis
- Embryo-fetal harm

Warnings and precautions
- Neutropenia
- Left ventricular dysfunction

COMMONLY REPORTED ADVERSE EFFECTS IN DESTINY-GASTRIC01 TRIAL

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Trastuzumab deruxtecan (n = 125)</th>
<th>Physician’s choice chemotherapy (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Nausea</td>
<td>63%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>60%</td>
<td>17%</td>
</tr>
<tr>
<td>Anemia</td>
<td>58%</td>
<td>38%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55%</td>
<td>9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26%</td>
<td>0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>22%</td>
<td>0%</td>
</tr>
</tbody>
</table>

IHC, immunohistochemistry; ISH, in situ hybridization.
More Can Be Done for Asian American Lung Cancer Patients

A RECENT STUDY led by the National Cancer Institute (NCI) showed that lung cancer deaths have dropped steadily since 2001.¹ Death rates for the most common form of lung cancer, non-small cell lung cancer (NSCLC),² fell by about 3% every year from 2001 to 2013.³ The drop in mortality was even more pronounced – about 6% – from 2013-2016.¹ The decline was mostly attributed to reduced smoking rates, but NCI researchers suggested that there may be a correlation between increased survival and the use of medicines that target specific genetic alterations in lung cancer cells.¹

According to the authors, doctors began routinely testing people with metastatic non-small cell lung cancer (NSCLC) in 2013 for the alterations, or mutations, targeted by these drugs. The tests, known as biomarker tests, can help clinicians to determine which treatment options are more likely to be effective against a patient’s specific type of lung cancer.² The key molecular biomarkers that play a role in metastatic NSCLC – and for which there are matching FDA-approved targeted treatments – are EGFR, ALK, BRAF V600E, ROS1, NTRK, MET and RET.⁴ Testing for actionable biomarkers has traditionally been done on tissue biopsy samples, although blood tests are now available as an additional option.⁵

Expert guidelines recommend that all patients with metastatic NSCLC get biomarker testing to better identify their specific cancer type.⁶ For example, people of Asian descent are at a higher risk of developing metastatic NSCLC caused by a mutation in the EGFR gene.⁷,⁸ These mutations present in up to 50% of Asian patients were diagnosed with a common subtype of NSCLC called adenocarcinoma, compared to only 10%-15% of patients in the US and Europe.⁹ However, only 60% of Asian metastatic NSCLC patients in New York and 57% of patients in Los Angeles – two of the most heavily populated Asian American cities in the United States – are being tested for EGFR mutations.¹⁰

“Biomarker tests are critical in subsets of the population where we know certain lung cancer mutations like EGFR occur more often, such as in Asian Americans. We must educate these patients about their risk factors and the importance of biomarker testing as part of a complete lung cancer diagnosis,” said Elaine Shum, MD, Perlmutter Cancer Center at NYU Langone Health.
Many Asian Americans may not be aware of their lung cancer risk factors, including the higher prevalence of certain biomarkers, such as EGFR mutations, compared to other racial or ethnic groups. As the number of metastatic NSCLC cases and deaths continue to rise in some Asian American communities, a panel of lung cancer experts has identified several factors contributing to the disparity in this population. The panel, sponsored by AstraZeneca as part of the company’s “It’s Okay to Ask” educational program, convened in Los Angeles on January 15, 2020 and virtually on October 29, 2020 to discuss this problem. “It’s Okay to Ask” is designed to empower lung cancer patients and their caregivers to take a proactive approach to understanding their treatment options.

Social and Cultural Barriers to Care
Despite increased awareness of lung cancer in recent years, stigma and blame remain a challenge for patients. According to the panel, many Asian American lung cancer patients feel guilt or shame for missing work or for being unable to care for themselves and their family. The stigma of lung cancer can contribute to a sense of fatalism in both patients and their doctors — impeding timely and accurate diagnosis and treatment.

Cultural factors impact access to testing and treatment, panel members said. In many Asian communities, patients are socialized to accept information and instructions from their doctor without being actively involved. Patients may be reluctant to share their lung cancer diagnosis with family and friends because they don’t want to be a burden. Some adult children may be hesitant to tell elderly family members about a lung cancer diagnosis to shield them from emotional stress.

“In Asian culture, the stigma of lung cancer may make it more difficult for some patients to fully confront the disease. We must help these patients understand that lung cancer isn’t their fault, and that it’s okay to talk openly about the disease and get help,” said David Park, MD, St. Jude Heritage Health.

Asian Americans who are diagnosed with metastatic NSCLC face real challenges. Biomarker testing as part of a complete diagnosis for metastatic NSCLC patients may be a key to solving some of the racial and ethnic disparities in lung cancer mortality and survival. The panel set forth strategies to increase Asian Americans’ access to testing and treatment along the continuum of care:

• **Educate**: Provide patients and caregivers with culturally and linguistically tailored information, educational tools, awareness campaigns, and doctors who can speak to patients in their native languages

• **Empower**: Confront the stigma of lung cancer with science, educating Asian Americans about their increased risk of having EGFR mutations

• **Screen**: Implement lung cancer biomarker testing in communities with dense Asian American populations with limited healthcare access

Panelists:
Elaine Shum, MD,
Perlmutter Cancer Center at NYU Langone Health, New York
David Park, MD,
St. Jude Heritage Health, Fullerton, California
Young Kwang Chae, MD, MPH,
Feinberg School of Medicine at Northwestern Medicine, Chicago
Songchuan Guo, MD,
Icahn School of Medicine at Mount Sinai, New York
Kin Lam, MD,
Mount Sinai Beth Israel Medical Center and New York Presbyterian Hospital, New York

References

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FDA APPROVAL INSIGHTS NIVOLUMAB/CABOZANTINIB IN ADVANCED RCC

On January 22, 2021, the FDA approved nivolumab (Opdivo) and cabozantinib (Cabometyx) in advanced renal cell carcinoma (RCC). Toni K. Choueiri, MD, reviews the data from the phase 3 CheckMate 9ER trial (NCT03141177), in which the combination led to an improvement in overall survival, progression-free survival, and overall response rate versus sunitinib (Sutent).

LISTEN: https://bit.ly/3iVUsEH

ONCLEIVE® ON AIR PODCAST SPOTLIGHT

FDA APPROVAL INSIGHTS NIVOLUMAB/CABOZANTINIB IN ADVANCED RCC

ONCLEIVE® ON AIR FORECASTING FUTURE ADVANCES ACROSS ONCOLOGY

ONCLEIVE® ON AIR CAPITALIZING ON CELLULAR THERAPIES IN LYMPHOMA AND MYELOMA

ASSESSING THE ADVANTAGES OF ADJUVANT TARGETED THERAPY IN LUNG CANCER

Adjuvant osimertinib (Tagrisso) has become a new standard of care for patients with non-small cell lung cancer with tumors harboring EGFR exon 19 deletions or exon 21 L858R mutations. “The most recent relevant story is the role of oncogenic drivers in early-stage disease and addressing those,” David R. Spigel, MD, said in an interview with OncologyLive®. “Even if you’re a critic [who says osimertinib is not] ready for prime time in terms of change in how we approach care now for early-stage-disease—except I’d say stage III, which is certainly ready—you would accept [that] a lot is happening that’s exciting to see.”

Spigel, who is chief scientific officer, director of the Lung Cancer Research Program, and principal investigator at the Sarah Cannon Research Institute in Nashville, Tennessee, cautioned that the approval of osimertinib does not give license to bring other targeted therapies into the adjuvant setting without prospective research or replace other established standards.

READ MORE: https://bit.ly/3cInGvK
include the use of molecular testing, maintenance therapy, and lenalidomide maintenance or continuous therapy. This is a particularly useful regimen for an increasing number of patients with myeloma who progress on regimens for the treatment of metastatic colorectal cancer (CRC). Patients hate having their ports, and not needing IV access is incredibly important in the metastatic setting. Patients hate having their ports, they keep moving…forward and trying to find therapies for people that might develop severe COVID-19. Until everybody’s vaccinated—and until we have concrete guidelines for who will be vaccinated and when—we should keep moving…forward and trying to find therapies for people that might develop severe COVID-19. COVID-19 will be around for quite a while, so there’s plenty of work to be done in understanding how the disease will behave and how people react to it. The immediacy of the problem is daunting, but these trials are important for helping improve long-term outcomes and reduce the burden on the health care system.

Among the many hematologic malignancies, CLL seems to be on the front line now, especially in terms of the different therapies [available] and research [that is being done].”

“Bioengineering has come to the clinical table. It’s a message that it is not just pharmacy, biochemistry, and molecular biology, but also bioengineering that is going to help us really take the next steps in treatments for patients with cancer, as we look to create these platforms to really tease out the mechanisms that go across all of those disciplines.”
In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:

29% reduction in risk of PFS event* (HR: 0.71; 95% CI: 0.54, 0.93; P = 0.011): median PFS 48.2 vs 20.8 months for A+CHP and CHOP, respectively; primary endpoint.

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

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

Important Safety Information

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

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

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

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

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

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

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

- **Hematologic toxicities**: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma or previously untreated PTCL.

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

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

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

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

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

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

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

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

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

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

**Most Common (≥20% in any study)**

**Adverse Reactions**

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

**Drug Interactions**

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

**Use in Specific Populations**

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

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages and full Prescribing Information at adcetrispro.com.


NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
The most common adverse reactions (≥20%) in combination with CHP were anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

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

ADCIETRIS in combination with CHP was evaluated in patients with previously untreated, CD30-expressing PTCL, in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. Patients were randomized to receive ADICIETRIS + CHP or CHP alone for up to 8 cycles. ADICIETRIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHP. The trial included patients with a Karnofsky Performance Status of 30% or more. The primary endpoint was progression-free survival (PFS). All patients received CHP for 8 cycles as assigned in the trial.

A total of 448 patients were treated (222 with ADICIETRIS + CHP, 226 with CHP), with 6 cycles planned in 81%, in the ADICIETRIS + CHP arm, 70% of patients received 8 cycles, and 18% received 6 cycles. Primary prophylaxis with G-CSF was administered to 34% of ADICIETRIS + CHP-treated patients and 27% of CHP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the AdCIETRIS arm and in 4% of patients in the CHP arm, most often from infection. Serious adverse reactions were reported in 33% of ADICIETRIS + CHP-treated patients and 35% of CHP-treated patients. Serious adverse reactions occurring in ≥2% of ADICIETRIS + CHP-treated patients included febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), and sepsis (3%).

The most common adverse reactions observed ≥2% more in patients receiving ADICIETRIS + CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥1%) adverse reactions observed ≥2% more with ADICIETRIS + CHP were febrile neutropenia, abdominal pain, decreased appetite, dyspnea, edema, cough, dizziness, hypokalemia, decreased weight, and myalgia.

In recipients of ADICIETRIS + CHP, adverse reactions led to dose delays of ADICIETRIS in 25% of patients, dose reductions in 8% (most often for peripheral neuropathy), and discontinuation of ADICIETRIS with or without other components in 7% (most often from peripheral neuropathy and infections).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCIETRIS + CHP Total N = 223 % of patients</th>
<th>CHP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia *</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia *</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Lymphopenia *</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Thrombocytopenia *</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Mucositis</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Distress</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

### Table 7: Adverse Reactions, cont’d

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCIETRIS + CHP Total N = 223 % of patients</th>
<th>CHP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

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

The table includes a combination of grouped and ungrouped terms. CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone.

Additional Important Adverse Reactions

**Infusion Reactions**

In a study of ADICIETRIS in combination with CHP (Study 6, ECHON-2), infusion-related reactions were reported in 10 patients (4%) in the ADICIETRIS + CHP-treated arm. Two (1%) patients had events that were Grade 3 or higher events, and none (0%) events were Grade 4.

**Pulmonary Toxicity**

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

**Cardiac Toxicity**

In a study of ADICIETRIS in combination with CHP (Study 6, ECHON-2), non-infectious pulmonary toxicity events were reported in 5 patients (2%) in the ADICIETRIS + CHP arm. All events were pneumonitis.

**6.2 Post Marketing Experience**

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

**Blood and lymphatic system disorders:** febrile neutropenia.

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

**Hepatobiliary disorders:** hepatic toxicity.

**Infections:** PML, serious infections and opportunistic infections.

**Metabolism and nutrition disorders:** hyperkalemia.

**Respiratory, thoracic and mediastinal disorders:** noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ABVD (some with fatal outcomes).

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

**6.3 Immunogenicity**

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation in human serum 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 samples, sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADICIETRIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Patients with ChL and sALC in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patients sampled that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (62%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15%–20%, respectively.

Data

Animal Data

In an embryofetal developmental toxicity study, pregnant rats received 2 intravenous doses of 0.3, 1.0, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 8 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with and 10 mg/kg of the drug and included increased early resorption (>99%), post-implantation loss (>99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and multiloculated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with ChL or sALC who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

ADCETRIS may damage spermatogenesis and testicular tissue, resulting in potential genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility

Males

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD19-expressing PTCL (Study 6: EHELON-2), 91% of ADCETRIS + CHP-treated patients were age 65 or older. Among older patients, 74% had adverse reactions > Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 92% had adverse reactions > Grade 3 and 93% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 29% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CrCl < 30 mL/min). No dose adjustment is required for mild (CrCl 30–50 mL/min) or moderate (CrCl 10–30 mL/min) renal impairment.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

Fever/Neutropenia: Advise patients to contact their health care provider if a fever of 100.3°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

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

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

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

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

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

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

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

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcertris.com.
WHEN THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic started upending health care services throughout the United States a year ago, the oncology community moved quickly to develop guidance on selecting therapies and setting treatment schedules for many cancers to allow for less frequent in-patient visits to clinics and infusion centers.

Now, several therapeutic strategies adopted to cope with the exigencies of the moment are working so well that they could become new standards of care after the pandemic ebbs. These include shorter radiation schedules, broader adoption of oral therapies, and new combinatorial approaches.

RADIATION SCHEDULES
Some of these changes would likely have become common eventually in any case, but they were embraced more quickly and widely because of the pandemic, experts say. A prime example is hypofractionation in radiation therapy treatments. In April 2020, as radiation oncologists were still adjusting to COVID-19 protocols, the results of the FAST-Forward trial were published, showing that a 5-fraction schedule of adjuvant radiotherapy delivered in 1 week is noninferior in terms of local cancer control and is as safe as a standard 15-fraction regimen after primary surgery for patients with early-stage breast cancer.

“We are practicing in the midst of a global pandemic and all of our leadership are telling us, ‘Delay treatment and give the minimum number of treatments you need to help your patients.’ And, like a miracle, suddenly this wonderful 4000-patient randomized clinical trial is published and it illustrates that we can take our 3- to 4-week treatment regimen and compress it to 1 to 2 weeks,” said Benjamin D. Smith, MD, director of research for breast radiation oncology at The University of Texas MD Anderson Cancer Center in Houston, and chair of Clinical Affairs and Quality Council for the American Society for Radiation Oncology (ASTRO).

The phase 3, randomized FAST-Forward trial enrolled 4096 patients who had invasive carcinoma of the breast (pT1-3, pN0-1, M0) after breast conservation surgery or mastectomy. They were assigned to 40 Gy in 15 fractions over 3 weeks, 27 Gy in 5 fractions over 1 week, or 26 Gy in 5 fractions over 1 week to the whole breast or chest wall. The primary end point was ipsilateral breast tumor relapse, with noninferiority predefined as 1.6% or less excess for 5-fraction schedules (HR, 1.81).

At a median follow-up of 71.5 months (interquartile ratio, 71.3-71.7), relapse occurred in 79 patients: 31 in the 40-Gy group, 27 in the 27-Gy group, and 21 in the 26-Gy group. Hazard ratios for therapy compared with 40 Gy in 15 fractions were 0.86 (95% CI, 0.51-1.44) for 27 Gy in 5 fractions and 0.67 (95% CI, 0.38-1.16) for 26 Gy in 5 fractions. Five-year incidence of ipsilateral breast tumor relapse after 40 Gy was 2.1% (95% CI, 1.4%-3.1%); estimated absolute differences compared with 40 Gy in 15 fractions were −0.3% (95% CI, −1.0 to 0.9) for 27 Gy in 5 fractions and −0.7% (95% CI, −1.3 to 0.3) for 26 Gy in 5 fractions ($P = .00019$ vs 40 Gy in 15 fractions).

At 5 years, moderate or marked clinician-assessed adverse effects (AEs) in normal
tissue in the breast or chest wall were reported for 98 of 986 (9.9%) patients who received 40 Gy, 155 (15.4%) of 1005 of those who had 27 Gy, and 121 of 1020 (11.9%) who received 26 Gy. Across all clinician assessments from 1 to 5 years, odds ratios (ORs) vs 40 Gy in 15 fractions were 1.55 (95% CI, 1.32-1.83; \( P < .0001 \)) for 27 Gy in 5 fractions and 1.12 (95% CI, 0.94-1.34; \( P = .20 \)) for 26 Gy in 5 fractions. Patient and photographic assessments showed a higher risk of AEs for those who received 27 Gy vs 40 Gy but not for participants who had 26 Gy vs 40 Gy.

Smith said some radiation clinics have held off on using the new schedule, but MD Anderson and a number of other centers quickly adopted it. A British study found that for National Health Service patients, use of a hypofractionated regimen of 26 Gy in 5 fractions for breast radiotherapy soared from 0.2% of all sessions in April 2019 to 60.6% in April 2020.²

Smith said the speed with which the new schedule was adopted in the United States represents a sharp contrast from previous changes in radiation therapy practices. “The change from 6-and-a-half weeks of radiation to 4 weeks of radiation literally took more than a decade. There was much

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**SNAPSHOT OF PATIENTS WITH CANCER WHO CONTRACT COVID-19**

A registry that the American Society of Clinical Oncology launched in April 2020 captures real-time data about patients with cancer who are infected with coronavirus 2019 (COVID-19). These data were gleaned from information submitted by 52 practices.

\( N = 2291 \)

*Data cutoff: March 1, 2021*

Cancer types of patients with COVID-19

- Breast cancer
- Other cancer
- Lung cancer
- Multiple myeloma
- Colorectal cancer
- Non-Hodgkin lymphoma
- Prostate cancer
- Lymphoid leukemia
- Pancreatic cancer
- Head and neck cancer
- Kidney cancer
- Melanoma
- Chronic myeloid leukemia
- Bladder cancer
- Other leukemia
- Stomach cancer
- Uterine cancer

**Cancer stage at COVID-19 diagnosis**

- Solid tumors
- Disease-free
- Localized
- Regional
- Metastatic
- Hematologic malignancy

**Comorbidities of patients at COVID-19 diagnosis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>77</td>
<td>37%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>86</td>
<td>24%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>23%</td>
</tr>
</tbody>
</table>

**For more information**, hover over the QR code with your smartphone or visit the ASCO COVID-19 Registry Data Dashboard at [https://bit.ly/3pAqVSV](https://bit.ly/3pAqVSV)
COVID-19

Experts said in interviews. Many patients with rectal cancers, for example, started taking oral capecitabine (Xeloda) instead of infusional 5-fluorouracil (5-FU), in accordance with guidelines developed by medical organizations.

“During the pandemic it was an easy way to really push some of those oral regimens. I’m confident the usage of [capecitabine] went up pretty dramatically,” said Howard A. “Skip” Burris III, MD, chief medical officer and president of clinical operations at Sarah Cannon in Nashville, Tennessee, and a 2014 Giants of Cancer Care® award winner in the Drug Development category. He also served as president of the American Society of Clinical Oncology (ASCO) for the 2019-2020 term.

Burris said he expects the preference for oral drugs, where appropriate, will continue after the pandemic ends, as there is strong interest in new oral therapies generally. These include CDK4/6 inhibitors that are being studied for use in the neoadjuvant and adjuvant setting for patients with hormone receptor-positive, HER2-negative breast cancer. The first oral taxane could be approved soon and oral checkpoint inhibitors are in active development, Burris noted.

Chancellor Donald, MD, assistant professor of clinical medicine at Tulane University in New Orleans and chair of the American Society of Hematology (ASH) committee on practice, said many oncologists began prescribing oral capecitabine to patients with colon cancer rather than at-home 5-FU infusions; this precluded hospital visits to pick up and drop off ambulatory infusion pumps. However, given the compliance issues concerning oral drugs, Donald said he’s not sure what physicians will do once exposure to COVID-19 at clinics is less of a concern.

“You take out the pandemic, once you take out that driver on the other side of the scale when you talk about risk-benefit, it’s hard to predict which way it’ll go. If this pandemic isn’t protracted over years, I think people may start to maybe shift back toward their previous practice habits,” Donald said. Providers may be influenced by their individual experiences of whether telehealth approaches either improve or worsen outcomes in their patients who are given oral rather than intravenous drugs, he added.

At the University of Pennsylvania’s Abramson Cancer Center in Philadelphia, physicians switched out many patients with rectal cancers to capecitabine. They also converted most patients with estrogen receptor-positive breast cancers, who would usually receive traditional intravenous chemotherapy, to oral hormone therapies instead, as is commonly done in Europe, said Lawrence N. Shulman, MD, the center’s deputy director for clinical services and director of the Center for Global Cancer Medicine.

Shulman said Penn investigators had already been studying how to improve patient adherence when they are prescribed oral drugs to take at home. One small study (N = 10) used automated chatbot software to manage patients with gastrointestinal neuroendocrine cancer who were prescribed capecitabine and temozolomide (Temodar).4 “The chatbot checks in with the patient every day, tells them when to take their medicines, asks them how they’re doing, and so on,” Shulman said. The cancer center recently received a grant to continue that work.

“COVID has accelerated research in this area because it’s clearly even more important than it was before,” he said.

In the chatbot study, participant satisfaction was high, as was the reliability of the system’s algorithmic branching to provide accurate dosing information and symptom triage. Symptoms were accurately graded 100% of the time and there was appropriate self-management advice or provider triage 100% of the time. Average daily adherence (based on self-reporting) was 97.4%. Participants reported that 3 emergency department visits were avoided during the study period.3

NEW COMBINATIONS

Another shift in treatment of rectal cancers at Penn and many other centers has been toward total neoadjuvant therapy (TNT), in which patients undergo chemotherapy with chemoradiotherapy (CRT) before surgery, instead of having standard concurrent CRT followed by surgery and adjuvant chemotherapy (CRT plus A). TNT had been studied for years but was more fully embraced as a way...
to allow postponement of surgeries during the early days of the pandemic, Shulman said. “It turned out to be a good thing to do. We were obviously not the only ones in the country doing it; most people started doing it. But it accelerated the transition to that and made people understand it better and feel more comfortable with it. I think that’ll be something that sticks,” Shulman said.

A meta-analysis of data from 7 studies published in JAMA Network Open in December 2020 supports the use of TNT for patients with locally advanced rectal cancer. The pooled prevalence of pathologic complete response (PCR) was 29.9% (range, 17.2%-38.5%) in the TNT group compared with 14.9% (range, 4.2%-21.3%) in the CRT-plus-A group. TNT was associated with a higher chance of achieving a PCR (OR, 2.44; 95% CI, 1.99-2.98). No statistically significant difference in the proportion of sphincter-preserving surgery (OR, 1.06; 95% CI, 0.73-1.54) or ileostomy (OR, 1.05; 95% CI, 0.76-1.46) between recipients of TNT and CRT plus A was observed. In 3 studies that presented data on disease-free survival (DFS), patients who received TNT had significantly higher odds of achieving improved DFS (OR, 2.07; 95% CI, 1.20-3.56).³

**USE OF GROWTH FACTORS**

One commonly adopted change used to minimize the likelihood of hospitalization and reduce patients’ vulnerability to infections was expanded use of granulocyte colony-stimulating factors (G-CSF) after therapy to prevent febrile neutropenia. “In the setting of a pandemic, to have someone neutropenic is something that comes with great risk,” Donald said.

A National Comprehensive Cancer Network panel on hematopoietic growth factors recommended changing the threshold for prophylactic use of G-CSF from only patients deemed high risk (>20% risk of febrile neutropenia) to those considered intermediate (10%-20% risk of febrile neutropenia) or high risk.⁴

Additionally, the panel members suggested that G-CSF be considered in patients without risk factors for complication to accelerate recovery of absolute neutrophil count after hematopoietic cell transplant to minimize the need for hospitalization. They also said that frequent patient visits to clinics could be

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**COVID-19 in the Clinic Oncology Resources**

- **American Society of Clinical Oncology (ASCO)**
  - ASCO’s coronavirus 2019 (COVID-19) resource center functions as a gateway to special reports, journal articles, regulatory updates, and a portal to its registries for patients with cancer. Highlights include:
    - Road to Recovery Report—An in-depth article provides insights into changes in care delivery, research projects, and regulatory activity that likely will be needed as the pandemic wanes.[https://bit.ly/3qDwdgn](https://bit.ly/3qDwdgn)
    - Expert insights—More than 60 peer-reviewed journal articles, including original research and commentary, are available on the resource site, many of which are free of charge.[https://bit.ly/3bARS43](https://bit.ly/3bARS43)

- **American Society of Hematology (ASH)**
  - ASH is maintaining a website that provides advice, insights, webinars, and access to peer-reviewed articles from its publications and other journals. Offerings include:

- **American Society for Radiation Oncology (ASTRO)**
  - ASTRO has created an information center with answers to frequently asked questions, access to journal articles, and information on advocacy. Features include:
    - Clinical insights—Guidelines are available on a range of radiotherapy topics, including disease-specific recommendations for treating patients with head and neck, breast, lung, prostate, and rectal cancers during the pandemic.[https://bit.ly/3duOIPo](https://bit.ly/3duOIPo)

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**National Comprehensive Cancer Network**
- [https://bit.ly/3sAxBTO](https://bit.ly/3sAxBTO)
  - Resources include information for patients on maintaining care and getting vaccinated against COVID-19. Offerings for providers include:

**Physicians’ Education Resource®, LLC (PER®)**
- [https://bit.ly/3uDrDP](https://bit.ly/3uDrDP)
  - PER® has a library of enduring continuing medical education (CME) programs from its series, “COVID-19 and Cancer Care: What Oncologists Need to Know Today.” Additional offerings include:
    - Infusion therapy—“Medical Crossfire®: Foundations in Outpatient Administration of Infused Therapies for COVID-19: Keeping Patients Out of the Hospital is a live, interactive webinar that will be held on March 23.[https://bit.ly/3qBchMh](https://bit.ly/3qBchMh)

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avoided with 1 of 3 schedules of self-administered medication: daily filgrastim; long-acting pegfilgrastim 1 to 3 days post chemotherapy; or on-body injector pegfilgrastim (Neulasta Onpro) use 1 day after chemotherapy.6

Shulman’s institution liberalized its G-CSF guidelines. However, “I’m not sure that’s going to stick. I’m not sure it really needs to,” he said. Burris, on the other hand, thinks that expanded use of the growth factors “likely will stick around” because the treatment comes with minimal AEs and patients can administer it themselves.

LONG-TERM ADOPTION
The retention or abandonment of some of the changes made during the pandemic will depend on a number of factors, experts said, including any new evidence that emerges in the coming months and years. Burris noted that ASCO launched an oncology registry to capture patterns of COVID-19 symptoms among patients with cancer and to understand how the pandemic is affecting the delivery of cancer care and patient outcomes. CancerLinQ, ASCO’s big data initiative, should also provide some of that information, he said.

Burris and others also said that it is unclear how payer responses to abrupt, major shifts in therapeutic practice will affect their ongoing use of those changes. If payers want to support changes that require fewer in-person appointments, such as greater use of oral drugs instead of infusions or longer intervals between doses, they should consider alternatives to episodic payment systems, Burris said. The recent changes also support reimbursement for the value of care provided rather than for the drugs dispensed, he said.

Payers have encouraged use of take-home therapies and remote treatment by temporarily covering telemedicine at in-person appointment rates or by waiving patient cost-share.7 Shulman said that his institution has been discussing with payers how to continue these services after the pandemic, but that it remains to be seen how coverage will be handled in the long term.

In addition, the field of radiation oncology faces a major reckoning as clinics switch to 1- or 2-week treatment schedules instead of those lasting 4 or more weeks, Smith said. Revenues are already dropping and fewer medical students are entering radiation oncology, which could affect the availability of radiotherapy services, he pointed out.

For a full list of references, see the article at Onclive.com.
For women with HR+, HER2- MBC* who have visceral disease† or primary ET resistance‡

Survival doesn’t have to be at higher risk§

Indication
Verzenio® (abemaciclib) is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced or metastatic breast cancer (MBC): 6
• In combination with fulvestrant for women with disease progression following endocrine therapy

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

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

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

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.

Visceral disease† and primary ET resistance‡ are associated with higher risk. 1,4
*Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement. 5
†Visceral disease was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC. 5,7
‡Primary resistance was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC. 5,7
§Patients with higher-risk disease, defined as the presence of visceral disease or primary ET resistance, were included in the MONARCH 2 clinical trial. 8
ET=endocrine therapy; HER2=human epidermal growth factor receptor 2–negative; HR+=hormone receptor–positive; MBC=metastatic breast cancer.

Verzenio® (abemaciclib) 50/100/150/200 mg tablets twice a day
In HR+, HER2- MBC*

Verzenio is the only CDK4 & 6 inhibitor to achieve significant overall survival improvement in combination with fulvestrant regardless of menopausal status1,9

OS in ITT Population1,6

- Results are based on a prespecified interim analysis and are considered definitive1,10
- The percentage of deaths at the time of analysis was 47.3% (n=211) and 57.0% (n=127) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively1,10
- Primary endpoint of median PFS was met: 16.4 months (95% CI: 14.4-19.3) median PFS with Verzenio plus fulvestrant vs 9.3 months (95% CI: 7.4-12.7) with fulvestrant alone (HR=0.553; 95% CI: 0.449-0.681; P<0.0001)6
- The percentage of PFS events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively6

Study Design

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

*With disease progression following ET.
BID=twice daily; CDK4 & 6=cyclin-dependent kinases 4 and 6; DoR=duration of response; IM=intramuscular; ITT=intent-to-treat; mOS=median overall survival; ORR=objective response rate; PFS=progression-free survival; PO=orally.

Important Safety Information (cont’d)

Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.
Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.
Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.
Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.
In HR+, HER2- MBC*

Even women with worse prognoses achieved survival outcomes consistent with the overall study population\(^1\)

![WOMEN WITH VISCERAL DISEASE\(^1\) HAD](8.1 months longer mOS\(^1\)

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

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

![WOMEN WITH PRIMARY ET RESISTANCE\(^1\) HAD](7.2 months longer mOS\(^1\)

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

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

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

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

Important Safety Information (cont’d)

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

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

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

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

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

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
For women with HR+, HER2- MBC*

How could Verzenio make a difference for your patients with higher-risk† disease?

Learn more at VerzenioData.com

Important Safety Information (cont’d)

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

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

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

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

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

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

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

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

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

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

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*With disease progression following ET.
†Patients with higher-risk disease, defined as the presence of visceral disease or primary ET resistance, were included in the MONARCH 2 clinical trial. 8

References:

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VERZENIO® (abemaciclib) tablets, for oral use

Initial U.S. Approval: 2017

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

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

CONTRAINDICATIONS:
None

WARNINGS AND PRECAUTIONS
Diarrhea
Diarrhea occurred in 81% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 85% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

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

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

Neutropenia
Neutropenia occurred in 41% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

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

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

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

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

Hepatotoxicity
In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the VERZENIO and placebo arms, respectively. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of VERZENIO-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 ALT increased, median time to onset was 61 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

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

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

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

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

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

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

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

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

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

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

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

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

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 3). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, and anemia.
fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

**Venous Thromboembolic Events**

- Thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant.

**Additional Adverse Reactions**

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

### Table 1: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Category</th>
<th>VERZENIO plus Fulvestrant N=443</th>
<th>Placebo plus Fulvestrant N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Fulvestrant</td>
<td>Placebo</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>1</td>
</tr>
<tr>
<td>Nausea</td>
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<td>Abdominal Pain</td>
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<td>1</td>
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<tr>
<td>Vomiting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Fulvestrant</td>
<td>Placebo</td>
</tr>
<tr>
<td>Infections</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Fulvestrant</td>
<td>Placebo</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Category</th>
<th>VERZENIO plus Fulvestrant N=443</th>
<th>Placebo plus Fulvestrant N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**Creatinine Increased**

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

### DRUG INTERACTIONS

#### Effect of Other Drugs on VERZENIO

**CYP3A Inhibitors**

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

**Ketoconazole**

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

**Other Strong CYP3A Inhibitors**

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

**Moderate CYP3A Inhibitors**

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

**Strong and Moderate CYP3A Inducers**

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

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

**Risk Summary**

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

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

**Data**

**Animal Data**

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

#### Lactation

**Risk Summary**

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

**Females and Males of Reproductive Potential**

#### Pregnancy Testing

**Risk Summary**

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

**Contraception**

**Females**

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

**Infertility**

**Males**

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.
**Pediatric Use**

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

**Geriatric Use**

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

**Renal Impairment**

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

**Hepatic Impairment**

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

**OVERDOSAGE**

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

Rx only.

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

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AL HCP BS_M2 28JAN2020
Neoadjuvant Atezolizumab Elicits Impressive Responses in Resectable NSCLC

by LISA ASTOR

DATA FROM THE PRIMARY analysis of the LCMC3 trial (NCT02927301) showed that 21% of patients with resectable stage IB to IIB non–small cell lung cancer (NSCLC) who underwent surgical resection following neoadjuvant atezolizumab (Tecentriq) had a major pathologic response (MPR), as well as significant surgical outcomes with a high rate of R0 resection.

Findings from the phase 2 study were presented during the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.1

The updated analyses included 181 patients who were enrolled to the open-label, multicenter, single-arm trial. Select patients with stage IIB NSCLC, those with T3N2 or T4, were also included, although those with T4 disease due to mediastinal organ invasion were excluded. Jay M. Lee, MD, chief, Division of Thoracic Surgery at Ronald Reagan UCLA Medical Center in Los Angeles, California, noted during the briefing that LCMC3 is the largest immune checkpoint inhibition monotherapy trial to date in patients with resectable NSCLC.

The primary end point of the study was MPR, defined as 10% or fewer visible tumor cells, and was evaluable in 144 patients in the primary efficacy population. The pathological complete response (pCR) rate for this population was 7%.

Earlier findings from an interim analysis of the study, which included the first 101 patients, showed an MPR rate of 18% (95% CI, 11%-28%) in 82 evaluable patients and a pCR rate of 4.9%.2 By RECIST criteria, 6 patients had a partial response (7.3%), 72 had stable disease (87.8%), and 4 had progressive disease (4.9%).

The surgical population included 159 patients, of which 155 were evaluable for pathologic stage evaluation.1 Of these patients, 43% were downstaged following neoadjuvant treatment with atezolizumab and 19% were upstaged.

At 1 year, the DFS rate was 85% both in patients with stage I/II (n = 81) and stage III (n = 75) disease; at 1.5 years, the rates were 79% and 77% in the stage I/II and stage III groups, respectively (P = .88). The median follow-up for OS was 2.1 years. OS rates at 1 year were 92% in patients with stage I/II disease and 95% in those with stage III disease. At 1.5 years, the OS rates were 91% and 87% in patients with stage I/II and stage III disease, respectively (P = .45).

No new safety signals were reported with neoadjuvant atezolizumab. In 181 patients, preoperative grade 3/4 treatment-related adverse events (AEs) occurred in 6%
compared with 12.6% of 159 postoperative patients. Grade 3/4 immune-related AEs occurred in 2.0% and 7.5% of these patient populations, respectively. Two grade 5 AEs of cardiac death and disease progression occurred that were considered unrelated to treatment.

SURGICAL OUTCOMES

Patients received the first dose of atezolizumab for a median of 15 days (range, 1-82) after enrollment, and surgery was planned within a window of 30 to 50 days after initiating treatment. Eighty-eight percent of patients were able to undergo surgery within the protocol window, with 3 patients undergoing surgery only 8 days after the second cycle of atezolizumab. The median time from the end of cycle 2 (day 22) to surgery was 22 days (range, 11-74).

The median time outside of the window for the other 12% of patients was 8 days (range, 1-45). The reason for undergoing surgery outside of the protocol window was treatment related for 4 patients, because of other medical reasons for 6 patients, and for logistical reasons from the patient or surgeon for 9 patients.

“Our study distinguishes itself from historical and neoadjuvant chemotherapy trials in that surgery was performed within a tight protocol window, and surgery was allowed a lot earlier from the completion of neoadjuvant atezolizumab,” Lee explained.

Comparatively, most neoadjuvant chemotherapy trials offered surgery as early as 14 days after neoadjuvant therapy through as late as 56 days after the completion of treatment.

“More than half the patients underwent resection, with a minimally invasive approach utilizing advanced or robotic operation. And remarkably, only 15% of patients required conversion to thoracotomy,” Lee said.

Thirty-seven percent of patients received a robotic-assisted surgical approach and 17% had video-assisted thoracoscopic surgery while 46% ultimately underwent thoracotomy. The majority of patients (79%) received a lobectomy, 2% had a wedge resection, 1% had a segmentectomy, 6% had bilobectomy, and 9% had pneumonectomy. Five patients did not have any resection.

R0 surgical margins were achieved in 92% of patients, R1 in 4%, and R2 in 4%. “[These] findings are at least comparable, if not superior, to historical neoadjuvant chemotherapy [trials],” Lee commented (FIGURE). Intracoparative complications were rare in the LCMC3 trial, and all complications were successfully repaired. One patient had a bronchial complication and 4 had vascular complications. The length of hospital stay was 7.5 days (range, 2-68). Two deaths were observed following surgery, 1 within 30 days of the procedure because of a sudden death that was considered unrelated to treatment and 1 within 2.5 months of the surgery from pneumonitis that was possibly related to atezolizumab therapy.

These rates were comparable to historical findings with neoadjuvant cisplatin-based chemotherapy, and Lee said that the mortality rate was superior to historical outcomes.

Lee noted that the LCMC3 trial provides further clinical evidence for the ongoing placebo-controlled phase 3 IMPower030 trial (NCT03456063) of neoadjuvant atezolizumab in combination with platinum-based chemotherapy in patients with resectable stage II, IIIA, or select IIIB NSCLC followed by adjuvant atezolizumab or best supportive care.
Chemoradiation Combo Yields Promising Results in Unresectable, Locally Advanced NSCLC

by KEVIN WRIGHT

The combination of pembrolizumab (Keytruda) plus concurrent chemoradiation therapy showed antitumor activity in patients with unresectable, locally advanced, stage III non–small cell lung cancer (NSCLC), regardless of PD-L1 status or tumor histology, according to follow-up data from the phase 2 KEYNOTE-799 study (NCT03631784). Updated findings were presented during the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.

The study enrolled 216 patients with previously untreated, unresectable, pathologically confirmed stage IIIA-C NSCLC, with measurable disease per RECIST 1.1 criteria. Cohort A consisted of patients with both squamous and nonsquamous NSCLC, while cohort B included patients with nonsquamous NSCLC only.

All patients enrolled in the study received up to 17 cycles of pembrolizumab, administered at 200 mg 3 times per week. Patients in cohort A also received physician’s choice of either paclitaxel or carboplatin 3 times per week on cycle 1, and either paclitaxel or carboplatin once weekly with thoracic radiotherapy on cycles 2 and 3.

Patients in cohort B followed the same dosing schedule for pembrolizumab with the addition of pemetrexed or cisplatin on cycles 1 to 3 and thoracic radiotherapy during cycle 3.

The dual primary end points of the study were overall response rate (ORR), per RECIST v1.1 criteria, and the percentage of patients who developed grade 3 or higher pneumonitis.

After an additional 6 months of follow-up, an analysis was conducted that showed the ORR for cohort A (n = 112) was 69.6% (95% CI, 60.2%-78.0%), with 4 patients (3.6%) showing a complete response (CR). The median duration of response (DOR) for this patient population was not reached. However, 82.2% of patients (n = 31) had a response lasting 12 months or greater.

Response rates in cohort B (n = 61) were similar, with an ORR of 70.5% (95% CI, 57.4-81.5), including 3 patients (4.9%) who achieved a CR. Median DOR was not yet reached, although the DOR was 12 months or greater in 72.1% (n = 5) of patients. The median time to response was 2.1 months (range, 1.1-7.6) for cohort A and 2.2 months for cohort B (range, 1.8-10.3).

“Interestingly, in a substantial number of patients who had to discontinue treatment earlier, an ongoing control of the disease or an ongoing response was observed in some patients for a couple of months,” said Martin Reck, MD, PhD, head of Thoracic Oncology and the Clinical Trial Department within the Department of Thoracic Oncology at the Lung Clinic Grosshansdorf in Germany.

The 12-month progression-free survival (PFS) rate was 67.7% for cohort A, with a 12-month overall survival (OS) rate of 81.2%. Twelve-month PFS and 12-month OS rates for cohort B were 65.2% and 88.0%, respectively. Median PFS and median OS were not reached for either cohort.

Overall, 93.8% of patients in cohort A and 95.0% of patients in cohort B reported at least 1 treatment-related adverse event (TRAE). In total, 119 patients reported TRAEs of grades 3 to 5, with 54 patients discontinuing treatment due to TRAEs. Five patients experienced TRAEs that led to death.

“Moreover, 17 patients experienced grade 3 or higher pneumonitis, although Reck noted that most of these types of events were able to be resolved.”

“Among the most common types of treatment-related adverse events, 17 patients experienced pneumonitis, although Reck noted that most of these types of events were able to be resolved.”

REFERENCE
ARE YOU THINKING DEEP ENOUGH IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too

With each relapse, multiple myeloma becomes increasingly difficult to control. As the disease progresses, very few patients (less than 5%) experience a deep response. However, evidence suggests a deep response may be associated with improved PFS and OS. Therefore, shouldn’t a goal of treatment be to achieve a deep response in as many patients as possible?

The hope is that more patients may achieve a deep response with emerging therapies on the horizon.

Learn more about why depth of response matters in relapsed or refractory multiple myeloma. Visit ThinkDeepMM.com

OS=overall survival, PFS=progression-free survival
MOBOCERTINIB (FORMERLY TAK-788) demonstrated clinically meaningful benefit and a manageable safety profile in previously treated patients with metastatic non–small cell lung cancer (NSCLC) who have EGFR exon 20 insertion mutations, according to phase 1/2 data presented during the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.1

Findings from 2 cohorts of the study (NCT02716116) evaluating the agent were included in the analysis. The first comprised 114 patients with EGFR exon 20–mutant NSCLC who received prior platinum-based therapy (PPP cohort).

The second was an expansion cohort (EXCLAIM) and comprised 96 previously treated patients with EGFR exon 20–mutant NSCLC, 90% of whom had received prior platinum-based therapy.

As of the November 1, 2020, data cutoff, the confirmed objective response rate (ORR) was 28% (95% CI, 20%-37%) per independent review committee (IRC) assessment, and 35% (95% CI, 26%-45%) per investigator assessment in the PPP cohort. The median progression-free survival (PFS), via both IRC and investigator assessment, was 7.3 months.

In the EXCLAIM expansion cohort, the confirmed ORR was 24% (95% CI, 17%-35%) per IRC and 31% (95% CI, 23%-43%) per investigator assessment; the median PFS, via both IRC and investigator assessment, was 7.3 months.

Additionally, the safety profile of mobocertinib was consistent with the known profiles of other EGFR tyrosine kinase inhibitors (TKIs).

“Mobocertinib demonstrated meaningful clinical benefit in both the PPP and EXCLAIM cohorts and the efficacy was comparable between them,” said Caicun Zhou, MD, PhD, professor of medicine and director of the Department of Oncology at Shanghai Pulmonary Hospital and director of the Tongji University Medical School Cancer Institute in China.

EGFR exon 20 insertion mutations are present in approximately 5% to 12% of EGFR-mutated NSCLC tumors. This is a patient population for which no other approved targeted therapies exist, and data for first- and second-generation TKIs or chemotherapy show ORRs of approximately 10% to 15% and a median PFS of 3 to 5 months, Zhou explained.

Mobocertinib is a potent, small-molecule TKI specifically designed to selectively target EGFR exon 20 insertion mutations.1 The agent received breakthrough therapy designation from the FDA in April 2020 for patients with EGFR exon20 insertion–mutant metastatic NSCLC, whose disease has progressed on or after platinum-based chemotherapy.

Most recently, in October 2020, China’s Center for Drug Evaluation designated the agent as a breakthrough therapy for the same indication.2

The study was comprised of a phase 1 dose-escalation portion, which evaluated mobocertinib alone and in combination with chemotherapy, and a phase 2 expansion, which included 7 different cohorts, plus an extension cohort, aimed at investigating the antitumor activity of mobocertinib. Patients in both cohorts received 160 mg of mobocertinib once daily.

The primary end point for the study was confirmed ORR, as assessed by IRC, whereas secondary end points included safety, tolerability, and efficacy.

In the analysis of the PPP cohort, the median age was 60 years (range, 27-84), 66% were female, and 60% were of Asian descent. Thirty-two percent of patients had received at least 2 prior systemic lines of anticancer therapy (range, 1-7). Moreover, the median time on treatment was 7.0 months (range, 0-31).

In EXCLAIM, the median age of patients was 59 years (range, 27-80). Sixty-five percent of patients were female, 69% were of Asian descent, and 31% had more than 2 prior systemic lines of therapy (range, 1-4). The median time on treatment was 6.5 months (range, 0-14).

Among the PPP cohort, mobocertinib resulted in reductions of target lesion volume, with 82% of patients experiencing a reduction from baseline in the sum of target lesion diameter. Results were similar in the EXCLAIM cohort, with 80% of patients experiencing a reduction from baseline in the sum of target lesion diameter.

The presentation also included detailed first results of these cohorts with a data cutoff of May 29, 2020. The PPP cohort had a confirmed ORR of 26% per IRC (95% CI, 19%-35%) and 35% (95% CI, 26%-45%) per investigator assessment. The median PFS was 7.3 months by both IRC and investigator review.

In the EXCLAIM cohort, the confirmed ORR was 23% (95% CI, 15%-33%) per IRC and 32% (95% CI, 23%-43%) per investigator assessment; the median PFS was 7.3 months by IRC and 7.1 months by investigator assessment; and disease control rate of 77% per IRC.

Per IRC, 78% and 84% of patients in the PPP and EXCLAIM cohorts, respectively, had a duration of response lasting greater than 6 months.

Additionally, confirmed ORRs with mobocertinib were similar among all prespecified subgroups. In Asian versus non-Asian patients in the PPP cohort, the ORRs were 28% and 22%, respectively, whereas in the EXCLAIM cohort the ORRs were 24% and 20%, respectively.

In those who received prior immunotherapy versus those without in the PPP cohort, the ORRs were 25% and 28%, respectively, whereas this subgroup in the EXCLAIM cohort had ORRs of 21% and 24%, respectively.

Finally, those who received a prior EGFR TKI versus those who did not in the PPP cohort had ORRs of 21% and 28%, respectively. In the EXCLAIM cohort, these rates were 15% and 26%, respectively.

The safety profile observed in the analysis demonstrated that mobocertinib was manageable.

The most common grade 3 or higher adverse event was diarrhea (21%). Nineteen patients (17%) discontinued treatment, most commonly because of diarrhea (4%), nausea (4%), vomiting (2%), decreased appetite (2%), or stomatitis (2%).
CONFIRM Data Push Nivolumab Into Treatment Landscape for Relapsed Mesothelioma

by BRITTANY LOVELY

DATA FROM THE PHASE 3 CONFIRM trial support single-agent nivolumab (Opdivo) as an effective treatment approach for patients with previously treated malignant mesothelioma.

Results showed that the trial met both its coprimary end points of overall survival (OS) and progression-free survival (PFS), expanding the treatment armamentarium for patients with relapsed/recurrent disease, according to Dean Fennell, MD, who presented the findings during the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.1

In total, 332 adult patients with previously treated, unresectable, histologically confirmed metastatic mesothelioma were randomized to either nivolumab (n = 221) or placebo (n = 111). The median OS was 9.2 months (95% CI, 7.5-10.8) with nivolumab compared with 6.6 months (95% CI, 5.0-7.5) with placebo (HR, 0.72; 95% CI, 0.55-0.94; P = .02). Investigator-assessed PFS was 3.0 months with nivolumab versus 1.8 months with placebo (HR, 0.61; 95% CI, 0.48-0.77; P < .001).

"[Effective therapy] for relapsed mesothelioma is an unmet need and there have been no randomized phase 3 trials that have demonstrated overall survival [benefit] in the relapsed setting," said Fennell, a professor and chair of thoracic medical oncology at the Leicester Cancer Research Centre at the University of Leicester in the United Kingdom. “Nivolumab is deemed a safe and effective treatment and should be considered the new treatment option for patients with relapsed mesothelioma.”

Patients were eligible to enroll in the CONFIRM trial (NCT03063450) if they had mesothelioma, received at least 1 prior line of therapy, and had an ECOG performance status of 0 or 1. The target sample size was 336 patients. However, enrollment was stopped at 332 patients because of the coronavirus disease 2019 pandemic. Sufficient event and follow-up was feasible with the recruited participants, Fennell noted.

Patients were randomized 2:1 to receive 240 mg in 30-minute intravenous infusions of either nivolumab or placebo on day 1 of a 14-day cycle. The secondary outcomes were RECIST-determined PFS, response rate, and safety.

Patients who were heavily pretreated—124 patients (56%) in the nivolumab arm and 66 patients (59%) in the placebo arm received 2 prior lines of therapy.

Further primary end point data showed that the 12-month OS rates were 39.5% (95% CI, 32.5%-46.3%) with nivolumab versus 26.9% (95% CI, 18.2%-36.4%) with placebo. The 12-month PFS rates were 14.5% (95% CI, 10.2%-19.7%) and 4.9% (1.8%-10.6%), respectively. The OS data were immature, with only 232 events having occurred by the analysis out of the target of 291 events, Fennell said. PFS data were mature with 310 events over the target 284.

“The large majority of immunotherapy studies in relapsed mesothelioma were small phase 1b and 2 studies and the only phase 3 study (PROMISE-meso; NCT02991482) in relapsed mesothelioma unfortunately showed no difference in PFS and OS when comparing pembrolizumab (Keytruda) with single-agent chemotherapy,” Rina Hui, MBBS, PhD, clinical professor of medicine at the Westmead Clinical School of the University of Sydney in Australia, said in a discussion of the CONFIRM data.2

Patients were stratified by PD-L1 status. However, there was no statistically significant evidence to support the utility of PD-L1 tumor proportion score (TPS) as a predictive marker for patient selection. Fifty-six patients who received nivolumab and 24 who received placebo were classified as PD-L1 positive (TPS ≥ 1%), and 94 patients who received nivolumab were PD-L1 negative (TPS < 1%) compared with 60 who received placebo.1

The median OS for patients with PD-L1-positive disease was 8.0 months with nivolumab versus 8.7 months with placebo (HR, 0.95; 95% CI, 0.51-1.76; P = .864). For patients with PD-L1-negative disease, the median OS was 9.0 months versus 6.4 months, respectively (HR, 0.74; 95% CI, 0.51-1.08; P = .115).

In terms of safety, the outcomes were balanced between the 2 arms. Grade 3/4 adverse events (AEs) were reported in 45% of patients treated with nivolumab compared with 42% of patients who received placebo. Serious AEs were reported in 36% and 39%, respectively. Further, 5 (3.6%) deaths were reported in relation to a serious AE in the nivolumab arm and 4 (5.3%) were reported in the placebo arm.

OUTCOMES IN CONFIRM STRATIFIED BY HISTOLOGY

Participants in the CONFIRM trial were also stratified by epithelioid versus non-epithelioid histology.2 Eighty-eight percent of patients in each arm were identified as having epithelioid disease at baseline (TABLE3).

The median OS for epithelioid patients in the nivolumab arm (n = 195) was 9.4 months compared with 6.6 months for patients in the placebo arm (n = 98; HR, 0.71; 95% CI, 0.53-0.95; P = .021). The 12-month OS rates were 40.0% (95% CI, 32.6%-47.3%) and 26.7% (95% CI, 17.5%-36.8%), respectively.

For those with nonepithelioid disease, the median OS for patients in the nivolumab arm (n = 26) was 5.9 months compared with 6.7 months for patients in the placebo arm (n = 13; HR, 0.79; 95% CI, 0.35-1.79; P = .572). The 12-month OS rates were 34.6% (95% CI, 15.8%-54.3%) and 30.8% (95% CI, 9.5%-55.4%), respectively.1

Although Hui noted that the sample size for those with nonepithelioid histology may be too small to draw a conclusion of benefit, she would consider nivolumab for these patients in the salvage setting.

“The authors concluded that significant clinical benefit was observed in the
Updated Findings Show Durable Responses for Tepotinib in MET ex14-Altered NSCLC

by DENISE MYSHKO

TEPOTINIB (TEPMETKO) DEMONSTRATED durable clinical activity in patients with MET exon 14 (METex14)-altered non-small cell lung cancer (NSCLC) in updated data presented during the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer.1

Paul K. Paik, MD, clinical director at The Thoracic Oncology Service at Memorial Sloan Kettering Cancer Center presented updated results from subgroup analyses of treatment-naïve and previously treated patients in the phase 2 VISION study (NCT02864992). As of the data cut-off of July 1, 2020, 152 patients had at least 9 months of follow-up and were assessed for efficacy (cohort A).

Patients with advanced, EGFR/ALK wild-type, METex14 skipping NSCLC received oral tepotinib at 450 mg once daily. Investigators found that efficacy outcomes were consistent in patients who received prior platinum-based chemotherapy and/or immuno-oncology (IO) therapy.

In treatment-naïve patients from cohort A (n = 69), the overall objective response rate (ORR) was 44.9% (95% CI, 32.9%-57.4%), with a median duration of response (DOR) of 10.8 months (95% CI, 6.9-not estimable). Progression free survival (PFS) was 8.5 months (95% CI, 6.8-11.3).

In previously treated patients from cohort A (n = 83), the ORR was 44.6% (95% CI, 36.7%-53.0%), the median DOR was 11.1 months (95% CI, 9.5-18.5), and median PFS was 10.9 months (95% CI, 8.2-12.7).

In the overall population, the ORR was 44.7% (95% CI, 36.7%-53.0%), the median DOR was 11.1 months (95% CI, 8.4-18.5), and the median PFS was 8.9 months (95% CI, 8.2-11.2). Across all 3 groups, investigators reported no complete responses. They did report partial responses (PRs) for 44.9%, 44.6%, and 44.7% of patients in the treatment-naïve, previously treated, and overall populations, respectively.

“Tepotinib continues to demonstrate durable clinical activity across the lines of the first-line treatment for adult patients with unresectable malignant pleuropulmonary mesothelioma in October 2020. 3

Therefore, a lot of patients would not have made it to a subsequent line clinical trial, explaining why only 12% [of patients had this subtype] in the CONFIRM study.”

Investigators of the CheckMate 743 trial (NCT02899299) evaluated the first-line combination of nivolumab plus ipilimumab (Yervoy) versus chemotherapy in patients with malignant pleural mesothelioma. The combination was approved by the FDA as first-line treatment for adult patients with unresectable malignant pleural mesothelioma in October 2020. 3

Updated findings presented at the International Association for the Study of Lung Cancer 2020 Presidential Symposium showed an observed OS benefit with nivolumab and ipilimumab over chemotherapy in patients with epithelioid disease (n = 456) at 18.7 months (95% CI, 16.9-22.0) versus 16.5 months (95% CI, 14.9-20.5), respectively (HR, 0.86; 95% CI, 0.69-1.08). For those with nonepithelioid disease (n = 149), the median OS was 18.1 months (95% CI, 12.2-22.8) versus 8.8 months (95% CI, 7.4-10.2), respectively (HR, 0.46; 95% CI, 0.31-0.68).4

Based on results of ongoing first-line immunotherapy combination studies, there is still much to be learned about the sequencing of nivolumab in the second-line setting and beyond, Hui concluded. “For patients who had received platinum-based chemotherapy as first-line treatment, monotherapy nivolumab now can be considered as a treatment option in the second-line setting or third-line setting after second-line chemotherapy,” Hui said. “As [CONFIRM] was placebo-controlled, the question is whether nivolumab provides better outcomes than second-line single-agent chemotherapy or second-line gemcitabine with the VEGFR inhibitor ramucirumab [Cyramza]...What could be considered as salvage treatment if nivolumab and ipilimumab has been used in the first-line setting?”

Hui also stressed the importance of identifying predictive biomarkers to determine other salvage treatments.
of therapy, including in patients who had received prior lines of therapy, with METex14 skipping [non–small cell] lung cancer,” Paik said. Patients received 500 mg of tepotinib once daily until disease progression, death, or adverse event (AE) leading to discontinuation or withdrawal of consent (FIGURE).

In the efficacy population, patients had a median age of 73.1 years (range, 41-94), 76 were male (52.1%), 76 had a smoking history (52.1%), and 83 had received prior treatment for advanced or metastatic disease (54.6%). Seventy-four patients had received prior platinum-based chemotherapy for metastatic disease, either alone (n = 64) or in combination with immunotherapy (n = 10).

“The response rate was [approximately] 30% to prior therapy, which was similar if patients had received either prior platinum-based chemotherapy or immunotherapy plus platinum-based chemotherapy,” Paik said. Specifically, in patients who had received platinum-based chemotherapy, investigators reported 2 complete responses (2.7%) and 19 PRs (25.7%) and in those who had received combination therapy, 3 PRs (30.0%).

Notably, approximately 15.1% of patients had brain metastases at baseline.

Tepotinib was generally well tolerated across therapy lines, with patients experiencing mostly mild to moderate AEs and few discontinuations. The safety data comprised patients from cohort A and the confirmatory cohort C for a total of 255 evaluable patients. One-quarter of patients in the overall population experienced AEs of grade 3 or higher and 27 (11%) of patients discontinued treatment.

“The most common treatment-related adverse events were class effect for MET inhibition including peripheral edema in 54% of patients,” Paik noted. Peripheral edema of grade 3 or higher occurred in 7% of patients and rarely led to discontinuation (4%). Other common AEs include nausea, diarrhea, blood creatine increase, and hypoalbuminemia. The safety profile was consistent in patients who received prior therapy including those who received prior IO, study authors found.

Based on data from the VISION trial, the FDA granted accelerated approval to tepotinib on February 3, 2021, for the treatment of adult patients with NSCLC whose tumors have a mutation that leads to METex14 skipping.

In March 2020, the Japanese Ministry of Health, Labour and Welfare approved tepotinib for the treatment of patients with unresectable, advanced or recurrent NSCLC with METex14 skipping alterations.

For a full list of references, see the article at https://bit.ly/3d03zqP.
Investigators Focus Devimistat Study on Older Patients With AML

by DENISE MYSHKO

Devimistat (CPI-613), a small molecule that targets enzymes involved in cancer cell metabolism, holds promise for older patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) who typically have a poor prognosis with standard-of-care chemotherapy, investigators said. The drug is combined with chemotherapy in the phase 3 ARMADA 2000 trial (AML003; NCT03504410).1

Devimistat is directed at the mitochondrial tricarboxylic acid (TCA) cycle, inhibiting activity of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, enzymes that regulate glucose-derived and glutamine-derived carbons in the TCA cycle. Devimistat therapy results in decreased oxygen consumption in AML cells, sensitizing them to chemotherapy.2

In December 2020, the FDA granted devimistat a fast track designation for the treatment of AML, a decision that "underscores the pressing need to find new ways to combat this aggressive disease," according to Jorge Cortes, MD, principal investigator for the ARMADA 2000 trial.3

"There has been some work already in the clinic prior to this study that made us excited about this agent; it has shown increased activity from what you would expect from just chemotherapy," Cortes said in an interview with OncologyLive®.

Cortes, who is director of the Georgia Cancer Center at Augusta University, said research still has a way to go to improve outcomes for patients with AML. "This is a hard population to treat but we are confident we have a good chance of showing some benefit for the patient. These patients need something because the response rates with standard chemotherapy are very poor and, even for the patients who respond, they tend to lose their response very quickly and survival is very poor."

Overall, the 5-year relative survival rate for patients with AML is 28.7%, according to statistics from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program.4 The median age at diagnosis is 68 years. (FIGURE 1). Outcomes deteriorate for patients with AML as they age.5 Although patients may initially respond to therapy, more than 50% experience a relapse and are then likely to die within a year.2

ARMADA 2000 TRIAL DETAILS

The rationale for the ARMADA 2000 trial is based on findings from a phase 1 study (NCT01768897) that tested the addition of devimistat to cytarabine plus mitoxantrone in older patients with R/R AML. The study enrolled 67 patients with a median age of 60 years (range, 21-79); 54% were 60 years or older. The median level of blasts in the marrow was 43% (range, 4%-97%), and 72% of participants had not undergone prior salvage therapy.2

Among 62 evaluable patients, the overall response rate (ORR) was 50%, comprised of 26 participants with a complete remission (CR) and 5 with a CR with incomplete hematologic recovery (CRi). Median survival was 6.7 months. Patients achieving a CR or CRi had a median survival of 13.2 months. In participants over 60 years old, the CR/CRi rate was 47% (15 of 32 patients), with a median survival of 6.9 months. Historically, investigators said, only 33% of older patients reach a CR/CRi. They found the study regimen was well tolerated.2

The ARMADA 2000 trial is enrolling patients 50 years and older with R/R AML after prior standard therapies (FIGURE 2). Refractory disease is defined as failing to achieve CR/CRi after at least 1 cycle of an induction regimen containing an anthracycline, cytarabine, or fludarabine; or at least 2 cycles of a hypomethylating agent (azacitidine or decitabine) with or without venetoclax (Venclexta). Relapse is considered recurrent AML after CR/CRi has been reached on prior therapy.1

Devimistat will be assessed in

FIGURE 1. Percent of New Cases by Age Group: Acute Myeloid Leukemia

Acute myeloid leukemia is more common in older adults; it is most frequently diagnosed among people aged 65 to 74 years, with the median age of diagnosis being 68 years.

Jorge Cortes, MD

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clinical trial in focus

aml

combination with high-dose cytarabine plus mitoxantrone (CHAM) compared with control therapy with 1 of 3 chemotherapy regimens. In the comparator arm, physicians can choose from: high-dose cytarabine plus mitoxantrone (HAM); mitoxantrone, etoposide, plus cytarabine (MEC); or fludarabine, cytarabine, and filgrastim (FLAG).

In the CHAM arm, devimistat is administered intravenously at 2000 mg/m² per day on days 1 to 5, along with cytarabine at 1 gm/m² on days 3 through 5, and mitoxantrone at 6 gm/m² every day following the first, second, and fifth doses of cytarabine.

In the comparator arm, the HAM regimen follows the same dosing for cytarabine and mitoxantrone. In the MEC regimen, etoposide is being given at 80 mg/m²; cytarabine at 1000 mg/m²; and mitoxantrone at 6 mg/m², all administered on days 1 through 6. The FLAG regimen is comprised of fludarabine at 30 mg/m² on day; cytarabine at 2 g/m²; and filgrastim at 5 µg/kg per day, all administered on days 1 through day 5.

The primary end point is CR. Secondary end points include overall survival (OS) and CRi. The trial aims to enroll 500 patients at about 50 sites in the United States, Canada, Europe, South Korea, and Australia. The trial is about 85% enrolled, and an interim analysis is expected in the second quarter of this year, according the developer, Rafael Pharmaceuticals, Inc.

research in other cancers

Because of its mechanism of action, investigators believe devimistat may be effective in other cancer types. Devimistat is being studied as a single agent and in combination regimens in multiple trials.

In solid tumors, studies are ongoing in metastatic colorectal and pancreatic cancers. A phase I/II study (NCT04593758) in R/R clear cell soft tissue sarcoma is planned but is not yet recruiting patients. In hematologic malignancies, the agent is being tested in R/R settings in myelodysplastic syndromes, T-cell lymphoma, and Burkitt lymphoma or high-grade B-cell lymphoma.

The most advanced of these studies is the phase 3 AVENGER 500 (NCT03504423) trial in which devimistat is being tested in combination with modified FOLFIRINOX (folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin) compared with FOLFIRINOX alone in metastatic pancreatic cancer. This trial, which has already recruited 500 patients, will assess progression-free survival as the primary end point. Secondary end points include OS, duration of response, and ORR.

In November 2020, the FDA granted a fast track designation to devimistat for the treatment of pancreatic cancer. Devimistat also has orphan drug designations for clear cell sarcoma, AML, pancreatic cancer, myelodysplastic syndrome, peripheral T-cell lymphoma, and Burkitt lymphoma. The compound has also received orphan drug designation for AML and pancreatic cancer from the European Medicines Agency.

references

MOLECULAR PROFILING HAS PAVED the way for several advances in the treatment of patients with gastrointestinal (GI) malignancies by identifying critical biomarkers and gene signatures that allow for new, more precise therapeutic options. As a result, the American Society of Clinical Oncology (ASCO) has chosen molecular profiling in GI cancers as the 2021 Advance of the Year in oncology.1

ASCO made the announcement as part of its "Clinical Cancer Advances 2021: ASCO’s Annual Report on the Progress Against Cancer." The report shines a light on important clinical milestones and policy developments that unfolded last year and identifies priorities for addressing unmet needs.

Although surgery, radiotherapy, and chemotherapy have served as the mainstay of treatment for GI cancers, these approaches have limited efficacy and can negatively affect quality of life, noted Sonali M. Smith, MD, editor in chief of Clinical Cancer Advances 2021, and colleagues. Development of more effective therapies was lagging until the introduction of molecular tumor analysis. "The ability to molecularly profile a GI tumor has expanded the treatment options for individual patients with GI cancers—extending survival while minimizing adverse effects," the authors said.

"Molecular profiling tools such as next-generation sequencing give us the ability to identify specific molecular- and genomic-targeted treatments that are likely to benefit an individual patient," ASCO Board Chairman Howard A. "Skip" Burris III, MD, FACP, FASCO, a 2014 Giants of Cancer Care® award winner, stated in a press release. "Personalized medicine is becoming a reality."

Specifically, the report cites new strategies for targeting HER2 and DNA mutation pathways as key developments in GI cancers. Positive clinical data have culminated in the FDA approvals of fam-trastuzumab deruxtecan-nxki (Enhertu) and pembrolizumab (Keytruda) for indications based on biomarkers.

Trastuzumab deruxtecan was approved for adults with locally advanced or metastatic HER2-positive gastric or gastroesophageal adenocarcinoma who have received a prior trastuzumab (Herceptin)-based regimen. The FDA granted the indication on January 15, 2021, based on findings from the phase 2 DESTINY-Gastric01 trial (NCT03329690), in which 188 patients were randomized 2:1 to receive the novel antibody-drug conjugate or physician’s choice of either irinotecan or platinum monotherapy.

For patients who received trastuzumab deruxtecan, the median overall survival was 12.5 months (95% CI, 9.6-14.3) compared with 8.4 months (95% CI, 6.9-10.7) for those who had chemotherapy (HR, 0.59; 95% CI, 0.39-0.88; P = .0097). The objective response rate (ORR) was 51.3% for the trastuzumab deruxtecan arm versus 14.3% for the chemotherapy arm.

Although HER2-targeted therapies have been part of the treatment landscape for HER2-positive gastric and gastroesophageal cancers, trastuzumab deruxtecan combines an anti-HER2 antibody with a therapy aimed at the DNA repair mechanism. Essentially, trastuzumab deruxtecan delivers a "highly targeted payload of the replication-interrupting drug into tumor cells, further triggering cell death," the authors said.1

Additionally, the agent has shown early signs of efficacy in patients with previously treated HER2-expressing unresectable or metastatic CRC, according to findings presented during the 2020 ASCO Virtual Scientific Program. Data from the phase 2 DESTINY-CRC01 study (NCT03384940) showed that trastuzumab deruxtecan monotherapy resulted in a 45.5% ORR (95% CI, 31.6%-59.6%), including 1 complete response, among 53 patients characterized as HER2 positive with an immunohistochemistry (IHC) score of 3+ or IHC 2+/in situ hybridization-positive.

In June 2020, the FDA approved pembrolizumab for the first-line treatment of patients with unresectable or metastatic colorectal cancer (CRC) that is microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR). The PD-1 inhibitor previously was approved for CRC that is MSI-H or dMMR with progression after chemotherapy.

The new indication was based on results from the phase 3 KEYNOTE-177 trial (NCT02563002), in which patients were randomized 1:1 to receive pembrolizumab or physician’s choice of combination chemotherapy.

Findings showed that pembrolizumab doubled median progression-free survival—16.5 months (95% CI, 5.4-32.4) compared with 8.2 months (95% CI, 6.1-10.2) for chemotherapy, for a 40% reduction in the risk of disease progression or death (HR, 0.60; 95% CI, 0.45-0.80; P = .0004).

In addition to GI cancer advances, the ASCO report points out pivotal developments in several other malignancies. “Progress in cancer treatments over the past year provide improved therapy for cancers like breast and lung,” Smith, the Elwood V. Jensen Professor and chief of the Section of Hematology/Oncology at the University of Chicago Department of Medicine in Illinois, said in a press release. “We also saw new treatment options for patients with difficult-to-treat cancers, such as bladder and nasopharyngeal cancers.”

In addition to cancer advances, research priorities listed in the report include developing strategies that predict response and resistance to immunotherapies, optimizing multimodality approaches to treating solid tumors, reducing the impact of obesity on cancer incidence and outcomes, and improving methods of detecting potentially malignant tumors. ■

REFERENCE
IN HER2+ EARLY BREAST CANCER (EBC), UNDERSTAND HER RISK OF RECURRENCE

HER2 = human epidermal growth factor receptor 2.
HER RISK OF RECURRENCE REMAINS, EVEN AFTER NEOADJUVANT TREATMENT

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.1,2

The CTNeoBC pooled-analysis assessed the risk of recurrence following neoadjuvant treatment among patients with breast cancer, including HER2+ EBC, based on historic data.

The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.1

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.1
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease. This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.

**Association between pCR and event-free survival (EFS)** in the HER2+ subgroup analysis of the CTNeoBC study

![Graph showing association between pCR and event-free survival (EFS)](image)

- **EFS** was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.¹

1,989 patients with HER2+ tumors were included in the subgroup analysis. 55% of which did not receive a full year of adjuvant HER2-targeted monotherapy treatment.¹

**While there are different paths you can choose for your patient with HER2+ EBC, her treatment shouldn’t stop at neoadjuvant therapy.**
Discover possible adjuvant treatment options that may be right for her*:

For patients who achieve pCR, visit
PCRinEBC.com

For patients who do not achieve pCR, visit
NoPCRinEBC.com

*There may be other treatment options available for your patients.

DESPITE MANY DIVERSITY INITIATIVES over the past 10 years, a lack of meaningful representation of certain racial and ethnic minorities continues in the oncology workforce, experts say. Achieving diversity will require hospitals and medical schools to move beyond current programs and address more challenging issues such as conscious and unconscious bias. Medical schools will need to welcome, attract, retain, and enhance a diverse student body, and hospitals will have to do the same for those who are already physicians practicing in oncology.

Diversity in the workforce is important for many reasons that go beyond racial and ethnic identification, oncology leaders say. “We want different opinions, different tactics for therapy, and different expertise and knowledge that can help our patients. It’s not about the color of their skin but about the diversity in their background and their expertise and what they bring to the table,” Shibu Varghese, MA, senior vice president of people and business operations and chief diversity officer, at The University of Texas MD Anderson Cancer Center in Houston, Texas, said in an interview.

The value of having a racially and ethnically diverse workforce in health care fields has been established on a national policy level since a 2004 report from the Institute of Medicine (now the National Academy of Medicine) advocated for broad changes that would improve participation for members of underrepresented minorities. These groups were defined as populations whose presence in the health care ranks does not reflect US demographics.¹

Scientific evidence supports the importance of diversity among health care professionals, the panel reported, saying that greater diversity “is associated with improved access to care for racial and ethnic minority patients, greater patient choice and satisfaction, better patient-provider communication, and better educational experiences for all students while in training.”¹

A diverse workforce allows oncology care providers to engage and increase participation among patients and build trust within various communities—a goal that should be prioritized, said Robert Winn, MD, director of Massey Cancer Center at Virginia Commonwealth University, in Richmond.

“In addition to this drive to look at basic and translational science, in addition to coming up with new molecules and medicines, we also ought to be thinking about the practice of reengaging and being involved with our communities to rebuild their trust,” he said in an interview. “It’s great to come up with a molecularly targeted therapy. It’s great to come up with immunotherapy. It’s great to come up with a vaccine for COVID-19 [coronavirus disease 2019]. But if it doesn’t go into people’s arms, you’re only helping some and not all.”

People of color have a long history of distrust of the medical system because of perceptions of racism. For example, findings from a study among residents of predominantly Black neighborhoods in Chicago about breast cancer treatment found mistrust and perceptions of racism and neglect.² Some participants cited the Tuskegee syphilis
study, which was conducted by the US Public Health Service in Tuskegee, Alabama, from 1932 to 1972 to examine untreated syphilis in Black men. Even when penicillin became available in 1947 to treat syphilis, treatment was withheld from participants.3

Patients tend to develop trust and a comfort level with providers of a similar background, Karen M. Winkfield, MD, PhD, executive director of the Meharry-Vanderbilt Alliance, in Nashville, Tennessee, said in an interview.

“It’s been shown that individuals who have similar backgrounds to the provider taking care of them do better. They feel better about their communications, and they are more willing to accept what the doctor is saying.”

THE ONCOLOGY WORKFORCE TODAY

In the oncology field, progress has been made in terms of diversity, but the workforce has not kept pace with the nation’s demographics. In 2019, just 3.1% of practicing hematologists and oncologists identified as African American compared with 13.4% of the US population, according to study findings presented at the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. For those of Hispanic ethnicity, the percentage was 3.6% compared with 18.3% of the population.4

A third group comprised of Native Americans, Alaskans, native Hawaiians, and Pacific Islanders represented 0.2% of the oncology/hematology workforce compared with 1.5% of the population.4

Overall, 12,826 physicians were actively practicing as medical oncologists, hematologic oncologists, or hematologists in 2018.5 The numbers of underrepresented minorities who are part of that workforce marked an improvement over statistics reported in 2015, when just 2.3% of practicing oncologists identified as Black or African American and just 3% as Hispanic or Latino, according an ASCO report.6

Nevertheless, these minority groups are forecast to grow as a percentage of the overall US population; by 2020, people identifying as Black or African American are expected to comprise 17.9% of the population and those of Hispanic or Latino origin are expected to make up 28.6%.7

Oncology professionals say medical institutions should amplify their efforts to increase students’ exposure to oncology and address challenges minority students face in the educational system as a whole.

One such challenge is conscious and unconscious bias, which exists at all levels in medicine, Winn pointed out. Early in his career, Winn, who is Black, said that he was mistaken for a maintenance worker, and that some patients expressed discomfort at having him as their physician.

“People are still surprised that I am a scientist or that I am a cancer center director,” he said. “My entire career from when I was a medical student to even now has been littered with people being surprised. I don’t want a society that is color blind because that means ultimately you don’t see me. I do want a society that understands that being an African American or a woman or someone who is different doesn’t necessarily mean anything.”

Systemic racism disproportionately affects communities of color, Winkfield said. “It starts with kids in K-12. We need efforts that help to set them up for success later on, providing the tool sets to advance to college. Once they are in college, there are ways to influence them to consider careers in medicine or science.”

Winn said his aspiration is that the oncology workforce will look like the diversity that exists in America. “I’ll recognize it when we don’t run away from our differences but embrace the differences among us because we understand our core humanity is what keeps us together,” he said.

One hurdle for increasing workforce diversity in the oncology field is the fact that these specialties rank lower than other areas of medicine in recruiting fellows, Ana Velázquez Manana, MD, MS, a clinical fellow at University of California, San Francisco, said while presenting the workforce data at ASCO 2020.

The percentage of fellows from underrepresented minorities was 9.98% in hematology/oncology fellows in 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. For those of Hispanic ethnicity, the percentage was 6.1%.

“Minorities recruited to hematology/oncology fellowships did not significantly increase from 2006 to 2018, Manana said. “Minorities are underrepresented in all steps of the hematology oncology pipeline, when compared to the US population,” she said.

One reason for this continued underrepresentation is that minority students often are
not exposed to hematology/oncology or radiation oncology fields during their medical training, Narjus Duma, MD, a coauthor of the study, said in an interview.

“Many students make their decisions about which specialty they are going to apply to based on their exposure in the last 2 years of medical school,” said Duma, an assistant professor of medicine, hematology/oncology at the University of Wisconsin, Madison.

Medical students often choose primary care. An Association of American Medical Colleges survey found that 41% of Black or African American physicians, 36.7% of Hispanic physicians, and 41.5% of Native American or Alaska native physicians practice primary care.

THE NEED FOR MENTORS AND ROLE MODELS

Winkfield said role models willing to reach students at all educational levels are needed. “It’s important to know there are people who look like you who are doing really good things and working in oncology and making a difference in their community. That could be something that encourages people to consider a career in oncology,” Winkfield said.

Duma is working to be a force for change. She speaks at local high schools and is cofounder of the Latinas in Medicine Group, which was established in 2019. The organization, which promotes the advancement of Latinas in medicine and has more than 5000 members, will soon launch its first study evaluating the Latinas in Medicine experience during medical training.

“It is, unfortunately, a vicious cycle: There are few oncology role models and mentors for minority students so minority students are pulled to other specialties in which there are more role models and more mentorships,” Duma said. “It’s important to have a mentor who knows how to navigate obstacles. Academic medicine is a wonderful place, but it has a lot of challenges. Having someone understand the cultural differences can help you deal with that heavy emotional load that we often have.”

MD Anderson Cancer Center is another institution that has made a commitment to diversity and inclusion. About 14 years ago, the organization formed a diversity council to provide input on policies related to inclusion in all aspects of the workforce; they also established an employee advisory council that represents the employees at large. Additionally, 2 years ago, MD Anderson put in place a policy that required managers to consider a diverse pool of candidates for each position and required training on unconscious bias.

With focused intention and support from our executive leadership, the institution has increased gender diversity and minority inclusion among the president’s direct reports, as well as in roles of vice president and above. Varghese said one of the organization’s goals is to develop partnerships with historically Black colleges and universities and high schools in underserved communities.

“A lot of what we have done in the past 10 years is look at hiring practices but that is limited by the lack of high school students who were interested in and prepared for careers in medicine and research,” he said.

MD Anderson has developed relationships with high schools and colleges in underserved communities and partnered with industry to help advance science, technology, engineering, and math programming.

In 2017 MD Anderson created an initiative, called The Partnership for Careers in Cancer Science and Medicine (PCCSM), to attract students to pursue careers in oncology with specific emphasis on students from underrepresented groups in science and medicine. The PCCSM partners with local high schools, programs, colleges, and medical schools to encourage students who have a strong interest in biomedical disciplines but may be limited by traditional selection methods. These students are often underrepresented minorities, from low-income families and/or first-generation college students.

The 2020 program was cancelled because of the COVID-19 pandemic, but during the four years the program has been offered—2017, 2018, 2019, 2021—MD Anderson has had a total of 127 participants (39 high school students; 76 college students, 12 medical students). Each year the program has grown to include more students, starting with 11 in 2017 and expanding to 51 in 2021.

These were composed of 86% underrepresented minorities (42% Black and 44% Hispanic) with 73% being female.

“Several studies have shown that diverse teams better address the toughest challenges and produce better outcomes than homogeneous teams, including in medicine and science,” Varghese said. “The lack of diversity in the cancer research workforce could impede our efforts to find innovative and ground-breaking solutions for a disease that touches 1 out of 4 Americans. Therefore, increasing the diversity in the oncology field is critical to sustaining our competitive edge over cancer.”

ASCVO’S COMMITMENT TO DIVERSITY

ASCO has committed more than $1 million to increasing diversity in the oncology workforce and engaged in efforts such as providing clinical research oncology rotations for medical students and providing residents with the opportunity to attend the ASCO Annual Meeting.

Starting in 2008, ASCO formed a Diversity in Oncology Initiative, convening a Health Disparities Committee task force in 2015.
that developed a strategic plan for racial/ethnic workforce diversity. Then in 2017, ASCO increased its commitment to diversity by developing a strategic plan to create more opportunities in oncology for minority populations and help address the barriers people from underrepresented minorities may face.

These efforts built upon the ASCO Diversity Mentoring Program, which was designed to encourage medical students and residents from racial and ethnic populations that were underrepresented in medicine to pursue careers in oncology. It has since matched 80 medical students and residents with mentors and is working to launch the 2020-2021 Diversity Mentoring Program.

More recently, in February 2021, ASCO appointed Sybil R. Green, JD, MHA, RPh, as diversity and inclusion officer, a new position, to help achieve the organization’s goals of equity, diversity, and inclusion. ASCO also established an internal Equity, Diversity, and Inclusion Task Force to examine potential inequities in the workforce. Green currently serves as the task force’s cochair.

Michael P. Kosty, MD, director of graduate medical education programs at Scripps Clinic and Scripps Green Hospital and medical director of the Scripps Green Cancer Center, both in La Jolla, California, is optimistic about achieving diversity in the oncology workforce.

Kosty helped develop ASCO’s Workforce Information System, and he said data gathered for a recent workforce report suggest that movement is occurring.

“There is increasing awareness and sensitivity toward issues of race and diversity,” he said. “Up and down the continuum of training, there have been efforts both at the national level and state levels and at institutions and colleges and medical schools to enhance and increase the number of underrepresented minorities going into medicine in general and specialty care in particular.”

REFERENCES
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UKONIQ is a targeted kinase inhibitor of PI3K-DELTA and CK1-EPSILON.

**INDICATIONS**

UKONIQ is indicated for the treatment of adult patients with:

- **MZL**
  - Relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen

- **FL**
  - Relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy

These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**Severe Cutaneous Reactions:** Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade. Provide supportive care as appropriate.

**Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5:** UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons, frequently in patients who also have aspirin hypersensitivity.

**Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose.

**Serious adverse reactions included** in 18% of 221 patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

**The most common adverse reactions (≥15%), including laboratory abnormalities, in 221 patients who received UKONIQ were increased creatinine (79%), diarrhea-colitis (58%), fatigue (41%), nausea (38%), neutropenia (33%), ALT increase (33%), AST increase (32%), musculoskeletal pain (27%), anemia (27%), thrombocytopenia (26%), upper respiratory tract infection (21%), vomiting (21%), abdominal pain (19%), decreased appetite (19%), and rash (18%).**

**Lactation:** Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose.

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

**IMPORTANT SAFETY INFORMATION**

**Infections:** Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for Pneumocystis jiroveci pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

**Neutropenia:** Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 10^9/L (Grade 3-4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia.

**Diabetes or Non-Infectious Colitis:** Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., ≥6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis.

**Hepatotoxicity:** Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

**Lactation:** Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose.

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

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UKONIQ™ (umbralisib) tablets, for oral use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

1.1. Marginal Zone Lymphoma

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior line of CHOP-based regimen.

This indication is approved under accelerated approval based on overall response rate [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2. Follicular Lymphoma

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

This indication is approved under accelerated approval based on overall response rate [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Infections

Serious, including fatal, infections occurred in patients treated with UKONIQ. Infections occurred in 43% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular) [see Adverse Reactions (6.1)]. Monitor for any new or worsening signs and symptoms of infection. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose [see Dosage and Administration (2.2)].

Provide prophylaxis for Pneumocystis jirovecii pneumonia (PJP) during treatment with UKONIQ [see Dosage and Administration (2.2)]. Withhold UKONIQ in patients with suspected PJP of any grade and who persistently discontinue in patients with confirmed PJP [see Dosage and Administration (2.2)].

Monitor for cytomegalovirus (CMV) infection during treatment with UKONIQ in patients with a history of CMV infection. Consider prophylaxis, treatment, or both for the prevention of CMV infection, including CMV reactivation [see Dosage and Administration (2.2)]. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly [see Dosage and Administration (2.2)].

5.2. Neutropenia

Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia or higher in 9% of 335 patients and Grade 4 neutropenia developed in 9% [see Adverse Reactions (6.1)]. The median time to onset of Grade 3 or 4 neutropenia was 45 days. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil counts <1 × 10^9/L (Grade 3). Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia [see Dosage and Administration (2.2)].

5.3. Diarrhea or Non-infectious Colitis

Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 323 patients and Grade 3 diarrhea occurred in 9% [see Adverse Reactions (6.1)]. The median time to onset for Grade 3 diarrhea or colitis was 1 day (range: 1 to 23 months), with 75% of cases occurring by 2.9 months. For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved. Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, the overall response rate of 14% of patients. Adverse reactions which resulted in permanent discontinuation of UKONIQ in 25% of patients included diarrhea-colitis (6%) and transaminase elevation (5%). Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Adverse reactions which resulted in permanent discontinuation of UKONIQ in 25% of patients included diarrhea-colitis (6%) and transaminase elevation (5%). Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Adverse reactions which resulted in dose reductions in <4% of patients included diarrhea-colitis (4%), transaminase elevation (7%), neutropenia (5%), vomiting (5%), and upper respiratory tract infection (5%). The most common (≥15%) adverse reactions, including laboratory abnormalities, were increased creatinine, diastolic blood pressure, nausea, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite, and rash.

Table 1 presents the adverse reactions in the pooled safety population of 221 patients with marginal zone lymphoma and follicular lymphoma who received the recommended dosage.

UKONIQ N=221

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Edema</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions Reported (≥10%) in Patients With Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

UKONIQ N=221

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Any Grade a (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil decreased</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 grading system.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action [see Clinical Pharmacology (12.1)], UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of umbralisib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryofetal mortality, and structural abnormalities at maternal exposures (AUC) comparable to those in patients at the recommended dose of 800 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraceptive during treatment and for one month after the last dose [see Use in Specific Populations (8.1, 1.3)].

Table 2: Select Laboratory Abnormalities (>20%) That Worsened from Baseline in Patients with Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

UKONIQ N=221

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Any Grade (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil decreased</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 grading system.
were administered oral doses of umbilasib at 100, 200, and 400 mg/kg/day during the period of organogenesis. Malformations were observed at doses of 200 mg/kg/day (left palate) and 400 mg/kg/ day (left palate and nasopharyngeal fistula). Additional findings occurred starting at the dose of 100 mg/kg/day and included folded retina, delayed ossification of sternebrae and vertebrae, increased resorptions, and increased post-implantation loss. The exposure (AUC) at a dose of 100 mg/kg/day in mice is approximately equivalent to the human exposure at the recommended dose of 800 mg.

In an embryo-fetal development study in rabbits, pregnant animals were administered oral doses of umbilasib at 30, 100, and 300 mg/kg/day during the period of organogenesis. Administration at 300 mg/kg/day in rabbits is approximately 0.03 times the exposure in human patients at the recommended dose of 800 mg.

8.2. Lactation

Risk Summary
There are no data on the presence of umbilasib in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions from umbilasib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose.

8.3. Females and Males of Reproductive Potential
UKONIQ may cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating UKONIQ.

Contraception
Females
Advise female patients of reproductive potential to use highly effective contraception during treatment with UKONIQ and for at least 4 months after the last dose.

Males
Advise males with female partners of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose.

Infertility
Males
Based on the findings from mice and dogs, UKONIQ may impair male fertility [see Nonclinical Toxicology (13.1)]. Trend for reversibility was noted in dogs 30 days after the last dose.

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

8.5. Geriatric Use
Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, 56% of patients were 65 years of age or older, while 19% were 75 years of age or older. No differences in effectiveness or pharmacokinetics were observed between these patients and younger patients. In patients 65 years of age and older, 23% experienced serious adverse reactions compared to 12% in patients younger than 65 years of age. There was a higher incidence of infectious serious adverse reactions in patients 65 years of age or older (13%) compared to patients younger than 65 years of age (4%).

8.6. Renal Impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment [creatinine clearance (CrCl) 30 to 89 mL/min estimated by Cockcroft-Gault equation] [see Clinical Pharmacology (12.3)]. UKONIQ has not been studied in patients with severe renal impairment (CrCl < 30 mL/min).

8.7. Hepatic Impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST ≤ ULN or total bilirubin > 1.5 × ULN and any AST) [see Clinical Pharmacology (12.3)]. UKONIQ has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

14. CLINICAL STUDIES

14.1. Marginal Zone Lymphoma
The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205 (NCT02793583), an open-label, multi-center, multi-cohort trial. Patients with MZL were required to have received at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 69 patients with MZL (extranodal (N=38), nodal (N=20), and splenic (N=11)) were enrolled in this cohort. The median age was 67 years (range: 34 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, 7% were Other, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy. Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.3 months (range: 15.0 to 28.7 months). Efficacy results are shown in Table 5.

Table 5: Efficacy Results in Patients with MZL (Study 205)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>34 (49)</td>
</tr>
<tr>
<td>95% CI</td>
<td>37.0, 61.6</td>
</tr>
<tr>
<td>CR, n(%)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>PR, n(%)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>DOR</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>Range, months</td>
<td>0.0, 21.8</td>
</tr>
<tr>
<td>CI, confidence interval; CR, complete response; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; NE, not evaluable; PR, partial response.</td>
<td></td>
</tr>
</tbody>
</table>

- *Based on Kaplan-Meier estimation
- *Denotes censored observation

The median time to response was 2.8 months (range: 1.8 to 21.2 months). Overall response rates were 44.7%, 60.0%, and 45.5% for the 3 MZL subtypes (extranodal, nodal, and splenic, respectively).

14.2. Follicular Lymphoma
The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, multi-cohort trial (NCT02793583). Patients with relapsed or refractory FL were required to have received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3 FL, large cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 117 patients with FL were enrolled in this cohort. The median age was 65 years (range: 29 to 67 years), 36% were female, 60% were White, 4% were Black, 7% had Stage III-N disease, 38% had bulky disease, and 79% had a baseline ECOG performance status of 0 to 1. Patients had a median of 3 prior lines of therapy (range: 1 to 10), with 36% refractory to their last therapy. Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.1 months (range: 13.5 to 29.6 months). Efficacy results are shown in Table 6.

Table 6: Efficacy Results in Patients With Relapsed or Refractory FL (Study 205)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>50 (43)</td>
</tr>
<tr>
<td>95% CI</td>
<td>33.6, 52.2</td>
</tr>
<tr>
<td>CR, n(%)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>PR, n(%)</td>
<td>46 (39)</td>
</tr>
<tr>
<td>DOR</td>
<td>Median, months (95% CI)</td>
</tr>
<tr>
<td>Range, months</td>
<td>0.0, 20.9</td>
</tr>
<tr>
<td>CI, confidence interval; CR, complete response; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; PR, partial response.</td>
<td></td>
</tr>
</tbody>
</table>

- *Based on Kaplan-Meier estimation
- *Denotes censored observation

The median time to response was 4.4 months (range: 2.2 to 15.5 months).

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

Infections
Advise patients that UKONIQ can cause serious infections that may be fatal. Advise patients to immediately report any signs or symptoms of infection (e.g., fever, chills, weakness) [see Warnings and Precautions (5.1)].

Neutropenia
Advise patients of the need for periodic monitoring of blood counts and to notify their healthcare provider immediately if they develop a fever or any signs of infection [see Warnings and Precautions (5.2)].

Diabetes or Non-infectious Collitis
Advise patients that they may experience loose stools or diarrhea and should contact their healthcare provider with any persistent or worsening diarrhea. Advise patients to maintain adequate hydration [see Warnings and Precautions (5.2)].

Advise patients of the possibility of colitis and to notify their healthcare provider of any abdominal pain/distress [see Warnings and Precautions (5.2)].

Hepatotoxicity
Advise patients that UKONIQ may cause significant elevations in liver enzymes and the need for periodic monitoring of liver tests. Advise patients to report symptoms of liver dysfunction including jaundice (yellow eyes or yellow skin), abdominal pain, bruising, or bleeding [see Warnings and Precautions (5.4)].

Severe Cutaneous Reactions
Advise patients that UKONIQ may cause a severe skin rash and to notify their healthcare provider immediately if they develop a new or worsening skin rash [see Warnings and Precautions (5.5)].

Embryo-Fetal Toxicity
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)].

Advise females of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose [see Use in Specific Populations (8.3)].

Lactation
Advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose [see Use in Specific Populations (8.2)].

Infertility
Advise males of reproductive potential that UKONIQ may impair fertility [see Use in Specific Populations (8.3)].

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5
Advise patients that UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain susceptible persons [see Warnings and Precautions (5.6)].

Administration
Inform patients to take UKONIQ orally once daily at approximately the same time each day with food and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to crush, break, cut or chew tablets [see Dosage and Administration (2.2)].

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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Edison, NJ 08837

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US-UMS-2009114
IT WAS 5:00 PM on a Monday, and Andrew Pecora, MD, FACP, CPE, was just wrapping up his practice for the day when one of his nurses came to the door, asking if he could see one more patient.

“This is a 19-year-old that they just rolled in, and he’s on a stretcher,” Pecora recounted the nurse telling him in May 2019. “He’s in the room crying with his family.”

He walked in to see a patient with stage IV epithelioid sarcoma, along with a large soft tissue back mass that was leading into his spine. Pecora, division chief of skin cancer and sarcoma services at John Theurer Cancer Center (JTCC) at Hackensack Meridian Health in New Jersey, estimated that he was weeks away from dying.

The patient had an ECOG performance status of 4 with rapidly progressing bulky disease, and had progressed on tazemetostat (Tazverik), pazopanib (Votrient), surgery, chemotherapy with doxorubicin and ifosfamide, and involved field radiation. 1

The standard choice for this patient, Pecora said, would be hospice, “but not many parents want to hear that when it’s their 19-year-old on the stretcher.”

Pecora knew that there were early data with checkpoint inhibitors in sarcoma, but because the patient had epithelioid sarcoma, a rarer subtype, the information was even more limited. Relapsed/refractory epithelioid sarcoma in particular has a poor expected survival.

As part of a compassionate use authorization, the combination of nivolumab (Opdivo) and ipilimumab (Yervoy) was administered to the patient, and within 2 weeks he had responded to treatment followed by a positron emission tomography (PET)–negative complete remission. Once a second negative PET/CT scan occurred, the combination therapy was discontinued.

“This all happened that night—people stayed until like 10:00 PM,” said Pecora, adding that the patient was admitted to the hospital shortly after receiving immunotherapy. “His immune system turned on and started killing his cancer. Within 3 weeks [the mass] on his back almost evaporated. It was a miracle; his disease completely went away.”

COLLABORATION ADDS VALUE
The collaboration to save this young patient, who achieved a complete response by October 2019, is a byproduct of the Georgetown Lombardi Comprehensive Cancer Center Consortium, of which JTCC and Georgetown are both part. Georgetown was formally recognized as a National Comprehensive Cancer Center research consortium in 2019.

It had been an ambition of JTCC to be part of a National Cancer Institute (NCI)–designated comprehensive cancer center, and it was in Georgetown’s interest to expand its footprint, especially in acute leukemias and multiple myeloma, Pecora added.

The first step was putting a bone marrow transplant program at Georgetown, “and with the success of that
program, that gave us the confidence to work closer together," he reflected.

Pecora worked in tandem with Louis M. Weiner, MD, director of Georgetown Lombardi Comprehensive Cancer Center and the MedStar Georgetown Cancer Institute, to bring the 2 organizations together before applying to become a designated consortium.

“We’re one of the largest providers of cancer services, and we have always been a major contributor to advances in this field,” said Pecora. “But we wanted to go to the next level and become a recognized entity—both on translational science as well as clinical science. The way to do that was to be become part of an NCI-designated cancer center.”

The joint efforts feature work on phase 1 and beyond studies of novel cancer therapies. Both institutions also evaluate new technologies, as well as develop and launch research that will provide a greater understanding of the ways in which northern New Jersey and Washington, DC, populations are impacted by cancer.1

Michael B. Atkins, MD, deputy director of the Georgetown Lombardi Comprehensive Cancer Center and the Scholl Professor and vice chair of the Department of Medical Oncology at Georgetown University Medical Center, said the Consortium has also led to their institution having strong multiple myeloma and transplant programs and a growing leukemia program, and has allowed them to get involved in chimeric antigen receptor (CAR) T-cell therapy for patients with hematologic malignancies.

“That is something that will grow in the future to probably a broader cellular therapy service, [one] that involves the treatment of not only hematologic malignancies with cellular therapy, but solid tumors using tumor-infiltrating lymphocyte protocols that will hopefully soon be commercially available," said Atkins.

Both campuses have merged their clinical research efforts across various diseases, expanded their investigator-initiated clinical trials and, Atkins added, have expanded their bedside-to-bench reverse translational research protocols.

Moreover, Atkins cited Georgetown’s robust population science program as another way to collaborate with JTCC, which focuses on issues from cancer detection to cancer policy.

“Our Cancer Prevention and Control Program has been heavily focused on addressing the needs within our patient catchment area of Washington, DC, which has some of the highest rates of cancer of any region within the United States,” Atkins said. “Those are unique needs that are focused more on a particular set of minority communities. Although the population in New Jersey is different, we have begun the work of identifying their needs and establishing a framework for addressing them.”

Georgetown leaders are now working to set up a satellite population science-focused effort within JTCC to address the needs of the geographical area, which, he said, is a population with more Hispanic individuals, a heavy smoking history, and various cancer types.

But one of the larger mergers between the 2 groups comes from the experience with immunotherapy. Between JTCC’s robust cellular therapy efforts with CAR T-cell therapy in hematologic cancers, and Georgetown’s interest in expanding immunotherapy, the 2 groups felt they could combine their expertise to build one of the leading immunotherapy efforts on the East Coast.

“We will be able to not only provide standard-of-care, cellular therapies, but we’ll also be able to participate in industry-sponsored cellular therapy research of all different types, and develop our own investigator-initiated cellular therapy trials,” Atkins envisioned.

RESEARCH CONTINUES

Regularly, the 2 institutions interact through their 8 respective disease groups with monthly conference calls to review research portfolios, share updates with patients on studies, and discuss ideas for future clinical trials. While such conversations previously took place on traditional phone calls, the format turned virtual via Zoom and WebEx once the coronavirus disease 2019 pandemic hit.

“We also use those calls to discuss clinical cases that are potentially problematic and how we would best manage those patients,” Atkins explained. “Those calls function as virtual tumor boards to discuss what happened in a particular case that might help us better understand the biology of that particular disease and its response to a specific therapy, and to potentially use that information to design a clinical trial to address our working hypothesis.”

Biweekly discussions also take place with leaders of disease groups and cancer research programs to review institutional-only challenges and identify solutions and issues in melding clinical research efforts, and to present on investigator-initiated trials that could add correlative science.

“We’re doing lots of research efforts across the whole array of cancer, everything from prevention, early detection, to treatment of all forms of cancer,” Pecora said. “The Consortium is involved in a number of clinical trials together; we are truly working together to stamp out cancer. The fact is that we have a reach from northern New Jersey down to Washington in one of the most densely populated parts of the country so we can influence tens of millions of Americans.”

CASE IN POINT

During the 2019 Connective Tissue Oncology Society (CTOS) Annual Meeting in Tokyo, Japan, where Pecora and Toretsky were in attendance and talking science with other colleagues, they came to figure out why checkpoint inhibitors were effective in the young patient with sarcoma—and the paper was published in the Journal of Immunotherapy, of which Pecora is the lead author.

Because the patient’s tumor was INI1-deficient, it also had extensive cytotoxic T-cell infiltration, which is known to be a predictor of response to immunotherapy.3-5

For Atkins, who has been involved with immunotherapy for more than 3 decades and has been a key player in the development of nivolumab and ipilimumab in renal cell carcinoma and melanoma, it was gratifying to see the combination have an effect in epithelial sarcoma.

“We need to keep doing research to identify more tumors, and more biomarkers, that identify which subset of patients with
different tumors use these checkpoints to escape the immune response,” he said. In the *Journal of Immunotherapy* paper, the investigators concluded that combination immunotherapy warrants further exploration for patients with INI1-deficient sarcomas in the salvage setting, regardless of prior treatment, level of tumor mutational burden, and microsatellite instability status. Extent of disease and performance status may also be characteristics to disregard when deciding to give checkpoint inhibition to a patient with sarcoma.

Andre H. Goy, MD, physician in chief of Hackensack Meridian Health Oncology Care Transformation Service; chairman and chief physician officer of JTCC; Lydia Pfund Chair for Lymphoma, Academic Chairman Oncology-Hackensack Meridian School of Medicine; and professor of medicine at Georgetown University, said the Consortium showcases the importance of pushing the envelope to find actionable items even, and in particularly, in difficult situations.

“It highlights the power of fantastic outcomes when you find the Achillean heel of a given tumor, and fantastic power of the immune system as durable therapy,” Goy added. As of the 19-year-old’s last visit in June 2020, he had resumed normal activities. His sarcoma was asymptomatic.

“As, now, there’s a whole new bridge—literally a breakthrough treatment—and a disease that otherwise was 100% fatal in a young person. It’s an amazing story,” Pecora concluded. “Had we not been part of the Consortium, I wouldn’t have known Dr Turetsky, we wouldn’t have had those conversations, and we may not have treated this man this way. And, we clearly would not have been able to publish it with the underlying science elucidated. That’s the power of the Consortium.”

### REFERENCES


Building MOMENTUM for Patients with Myelofibrosis

If you are interested in learning more about the MOMENTUM Clinical Trial for Patients with Myelofibrosis and determining if your patients may be eligible, please contact a MOMENTUM Trial representative by visiting momentumtrial.com/for-physicians
Experts Take Stock of New CNS Data for HER2+ Metastatic Breast Cancer

by BRITTANY LOVELY

ALTHOUGH TOP-LINE DATA from clinical trials have fueled excitement across the therapeutic landscape for patients with HER2-positive metastatic breast cancer, disease progression and the development of central nervous system (CNS) metastases remain significant clinical challenges.1 Now, findings from recent analyses have kindled hope that novel agents with manageable toxicity profiles may begin to bridge the gap for this population.

Two tyrosine kinase inhibitors (TKIs), neratinib (Nerlynx) and tucatinib (Tukysa), have demonstrated efficacy against CNS metastases, according to findings presented at the 2020 San Antonio Breast Cancer Symposium (SABCS). Leading breast cancer investigators took a deep dive into these data during the OncLive® “HER2 Breast Cancer Talk” video program.

Neratinib, initially approved in 2017 as extended adjuvant therapy for early-stage, HER2-positive breast cancer, gained an expanded indication in February 2020 for use in combination with capecitabine (Xeloda) for patients with advanced or metastatic HER2-positive disease who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.2

The decision was based on data from the NALA trial (NCT01808573) in which the regimen showed a significant improvement in progression-free survival (PFS) versus lapatinib (Tykerb) plus capecitabine. The median PFS was 5.6 months (95% CI, 4.9-6.9) compared with 5.5 months (95% CI, 4.3-5.6), respectively (HR, 0.76; 95% CI, 0.63-0.93; P = 0.059). Median overall survival (OS) was 21 months (95% CI, 17.7-23.8) and 18.7 months (95% CI, 15.5-21.2), respectively (HR, 0.88; 95% CI, 0.72-1.07; P = 0.2086).2

In April 2020, the FDA approved tucatinib in combination with trastuzumab (Herceptin) plus capecitabine for patients in the third-line setting based on results from the HER2CLIMB trial (NCT02614794). The median PFS in patients receiving tucatinib was 7.8 months (95% CI, 7.5-9.6) compared with 5.6 months (95% CI, 4.2-7.1) for patients receiving trastuzumab plus capecitabine alone (HR, 0.54; 95% CI, 0.42-0.71; P < 0.0001). The median OS in patients on the tucatinib arm was 21.9 months (95% CI, 18.3-31.0) compared with 17.4 months (95% CI, 13.6-19.9).
The analyses from the phase 3 NALA trial are important in that they led to regulatory approval of neratinib and capecitabine. [We saw] improved PFS compared with lapatinib and capecitabine in patients who had received at least 2 lines of prior therapy for metastatic HER2-positive breast cancer.

Investigators allowed patients on the trial who had stable brain metastases, unlike HER2CLIMB, which enrolled patients who had untreated brain metastases [that] recurred after treatment. In this situation, patients had to have stable disease. What investigators saw, and had already presented and published, was that there were fewer CNS interventions required. [Data for the] 32 patients who had measurable CNS disease showed that the intracranial response went from 15.4% with [lapatinib plus capecitabine] to 26.3% with [neratinib plus capecitabine]. That’s a pretty impressive difference.

Investigators also were able to look at about 50 patients in each arm who had CNS metastases and saw an improvement in PFS. [Also,] in the overall intention-to-treat population, the OS was similar. They could not analyze that specifically in patients with CNS metastases, but if they looked at the patients receiving lapatinib and capecitabine despite the early transient presence of diarrhea in some patients.

HRQOL Data in the NALA Trial

- **Summary score**: HR, 0.94 (95% CI, 0.63-1.40; P=.7560)
- **Global health status score**: HR, 0.890 (95% CI, 0.63-1.39; P=.4992)
- **Physical functioning score**: HR, 0.759 (95% CI, 0.52-1.103; P=.1437)
- **Fatigue score**: HR, 0.909 (95% CI, 0.67-1.222; P=.522)
- **Constipation score**: HR, 1.337 (95% CI, 0.859-2.102; P=.199)
- **Diarrhea score**: HR, 1.709 (95% CI, 1.318-2.226; P=.0001)
- **TTD between treatment arms**: HR, 0.810 (95% CI, 0.527-1.241; P=.3298)

Conclusion: Health-related quality of life (HRQOL) was sustained with neratinib plus capecitabine therapy compared with lapatinib plus capecitabine despite the early transient presence of diarrhea in some patients.

- HRQOL was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–C30 (QLQ-C30, version 3), and the EORTC QLQ Breast Cancer Module.
- Time to deterioration (TTD) was defined as time from baseline to first assessment with a change in HRQOL score ≥ 10 points, which was considered clinically meaningful.
- The QLQ-C30 summary score and 6 scales:
  - **Summary score**: HR, 0.94 (95% CI, 0.63-1.40; P=.7560)
  - **Global health status score**: HR, 0.890 (95% CI, 0.63-1.39; P=.4992)
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The analyses from the phase 3 NALA trial are important in that they led to regulatory approval of neratinib and capecitabine. [We saw] improved PFS compared with lapatinib and capecitabine in patients who had received at least 2 lines of prior therapy for metastatic HER2-positive breast cancer.

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Investigators also were able to look at about 50 patients in each arm who had CNS metastases and saw an improvement in PFS. [Also,] in the overall intention-to-treat population, the OS was similar. They could not analyze that specifically in patients with CNS metastases, but if they looked at the patients receiving lapatinib and capecitabine versus 12.4 months in patients who were receiving neratinib and capecitabine, so that’s a pretty big difference of 4 months. [These data are] very concordant with data from the NEFERTT [NCT00915018] trial as well as a small consortium trial called TBCRC 022 [NCT01494662] and, of course, the data from ExteNET [NCT00878709]. Another interesting part of that presentation is that 3 patients had leptomeningeal disease. I always wonder how they got onto the trial, but they had leptomeningeal disease and 2 of them who were enrolled on the neratinib arm had a long time to progressive disease. It was really interesting. [The results showed] 9.8 months to progression and the OS was 19.8 months; that was for 1 patient. The other patient had 5.6 months to progression and a 17.4-month OS. [That’s really very impressive and we just don’t have a lot of data on leptomeningeal disease.]

Subset data for patients on TBCRC 022, also appeared to have some efficacy, but that wasn’t a randomized trial. It’s fascinating to see this long duration of disease control and OS when neratinib was included. To me, I thought that the data in the CNS [subset] group were impressive. [Although this was] not unexpected, the leptomeningeal disease, I think, was really important and contributory.

Another poster presentation looked at health-related quality of life [HRQOL] in the NALA trial, and that’s important when we start looking at a drug that we know causes diarrhea. How do people manage and how does their HRQOL pan out? Investigators looked at the QLQ-C30 [Quality of Life Questionnaire–C30], which is an EORTC [European Organisation for Research and
TUCATINIB
HER2CLIMB Study Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hormone receptor–positive disease</th>
<th>Hormone receptor–negative disease</th>
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<tbody>
<tr>
<td></td>
<td>Tucatinib + trastuzumab/capecitabine (n = 107)</td>
<td>Placebo + trastuzumab/capecitabine (n = 59)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>HR 7.5 (5.6-9.5)</td>
<td>5.1 (4.1-5.7)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.48; 95% CI, 0.31-0.75; P = .0008</td>
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<tr>
<td>1-year PFS rate (95% CI)</td>
<td>23.8% (12.6%-37.0%)</td>
<td>0%</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>HR 18.1 (14.4-NE)</td>
<td>12.8 (11.2-18.2)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.76; 95% CI, 0.46-1.26; P = .3</td>
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<tr>
<td>2-year OS rate (95% CI)</td>
<td>37.5% (19.5%-55.3%)</td>
<td>0%</td>
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CNS, central nervous system; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

HRQOL Data for Patients With CNS Metastases in the HER2CLIMB Trial

- Overall health status was evaluated using visual analogue scale (VAS).
- TTD of health-related quality of life (HRQOL) was defined as decrease of 7 points on VAS.
- Change from baseline was evaluated on individual patient-reported items including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- HRQOL data were available from 331 of 612 patients, including 164 patients with CNS metastases: 107 patients in the tucatinib arm and 57 patients in the placebo arm.

Conclusions:
- HRQOL was maintained throughout treatment and was not noticeably different between treatment arms in patients with CNS metastases.
- TTD was significantly delayed with tucatinib, as demonstrated by EQ-5D-5L health score: 49% reduction in the risk of deterioration (HR, 0.51; 95% CI, 0.28-0.93).
- Mobility, usual activities, pain/discomfort, and self-care worsened after treatment discontinuation in both arms for patients who started with moderate, severe, or extreme problems.

CNS, central nervous system; TTD, time to deterioration.

Fast Facts

- Evolve the concept of late-line treatments.
- Lapatinib/ capecitabine included in NALA regimen in later lines.
- Update to the approach to patients with brain metastases.
- NALA regimen in later lines.
- Updated options for patients with hormone receptor–negative disease.
- Updated options for patients with hormone receptor–positive disease.
- Tucatinib arm (n = 91) Placebo arm (n = 34)
  - Median PFS, months (95% CI): 7.8 (6.1-11.6) vs. 5.4 (2.9-8.6)
  - 1-year PFS rate (95% CI): 26.0% (14.2%-39.5%) vs. 0%
  - Median OS, months (95% CI): 18.5 (14.5-NE) vs. 11.5 (8.8-15.2)
  - 2-year OS rate (95% CI): 44.1% (28.7%-58.4%) vs. 0%

Treatments of Cancer] measure, and also HRQOL. In the global evaluation, patients treated with neratinib had a sustained HRQOL and they maintained their QLQ-C30 scores, which also were not worse. The only place where patients felt worse was with diarrhea; there was obviously a little bit more diarrhea, as you would expect, so you see a slightly higher score [FIGURE 1].

Overall, that didn’t translate into anything different in terms of the global scores. I thought it was quite impressive that in the trial, patients had more diarrhea, they didn’t have worse constipation, and that neratinib resulted in sustained HRQOL on this scale as well, which is about overall functioning.

Where do you see using the NALA regimen in your sequencing for metastatic HER2-positive disease?

I think that I’d probably use this regimen in later lines, after potentially using tucatinib. Maybe I’d use it before trastuzumab deruxtecan [Enhertu] in someone who has low disease burden in whom I was concerned about toxicities. I definitely think that there is a time and place to use it. Someone with CNS disease, perhaps, might warrant getting it, or someone who maybe had cardiac issues in whom you want to use antibody-free therapy. I think that’s a situation in which this combination would be [effective], particularly in that group of patients.

Some of these patients are getting so many different treatments [in their sojourn] that we need a lot of options. Margetuximab [Margenza] is now going to be available. Although it’s a crowded space, we need these drugs because these patients are living longer and longer, and many patients are getting the later lines of therapy.

I totally agree with Dr Tripathy. I think the patients with brain metastases will be quite compelling. I’ll use the tucatinib first, but I’ll use the doublet as well in the patients that Dr Tripathy described. Patients need continued options and I think what we see from the NALA data is that these were very heavily pretreated patients, and they will get improvement in their PFS over what used to be our standard late-line treatment, lapatinib and capecitabine. I will use neratinib/capecitabine instead.
impressive, so it’s worth discussing the numbers: 15.6% [in those with hormone receptor–positive disease] versus 45.3% in hormone receptor–negative disease.

The difference in patients with hormone receptor–positive disease was still more than 10%–27.1% [with placebo], and 37.4% [with tucatinib]—but when you looked at the PFS and OS, the PFS differences looked to be fairly similar. The hazard ratios were almost identical regardless of whether you had hormone receptor–positive or –negative disease: 0.54 and 0.58 in negative and positive disease, respectively, for PFS.

Then if you looked at OS, it’s interesting because the patients with hormone receptor–positive disease had a narrower difference in OS—although again, [the trial was] not powered to look at that numerically. Their 2-year OS rate was almost 10% greater if they got tucatinib versus placebo, and numerically there was a slight increase in OS.

However, for the hormone receptor–negative group, who tend to have more resistant disease, there was a dramatic difference in 2-year OS rate–17.3% versus 51.3% [for placebo versus tucatinib, respectively]—and the median OS was 14.1 versus 31.1 months, respectively. These just continue to be just stellar and amazing data.

Investigators also looked at the PFS by hormone receptor status for patients with baseline brain metastases, and it didn’t make any difference. If a patient had brain metastases, they had a big improvement in PFS regardless of hormone receptor–negative or –positive status. That was encouraging. You see that same differential trend in OS, with less benefit in hormone receptor–positive versus hormone receptor–negative disease, probably because those patients have more treatment options overall. Even the control group does a little bit better than the hormone receptor–negative group.

I thought these data were really, really helpful in understanding the differences in hormone receptor–positive and –negative disease, and [in understanding] the lack of differences and looking at the natural history of these patients as well. It was nicely done and part of the spotlight on HER2-positive disease at San Antonio.

Another poster looked at HRQOL in patients being treated with tucatinib on HER2CLIMB who had brain metastases, which I think is a fascinating subset because it was such a big subset in this trial. They saw a markedly longer and clinically meaningful time to deterioration of HRQOL [FIGURE 2].

As you would expect, you live longer, you have less progression, you have better response in the brain, so your HRQOL follows along with that. It’s not that toxicity is making it worse. That was really nice to see, and patients treated with tucatinib maintained their HRQOL throughout the treatment—again, much longer than patients treated with trastuzumab and capecitabine.

I think that these are encouraging data [to see] when we add a novel agent to patients. Obviously, OS is our gold standard, but it’s nice to have people live longer and not feel miserable. In this situation, I think we saw great, great data.

TRIPATHY

The tucatinib story for CNS disease and its overall impact on survival is great to see. It’s encouraging to see that its impact is sustained, and to see it in both hormone receptor–positive and –negative disease.

O’SHAUGHNESSY

That’s what I would highlight, too: with the tucatinib triplet, we finally have good agents [approved] or in progress for patients with brain metastasis. It’s quite outstanding. Additionally, the neratinib/capecitabine data [show that the regimen] also has salutary effects in the brain, so it’s a great advance for patients.

RUGO

So much excitement is going on in the whole field of HER2-positive disease...You see all these subset analyses in the longer follow-up subset of HER2CLIMB, and the longer follow-up data from both trastuzumab deruxtecan and that of the NALA trial. Also, you look at the effect on CNS metastases, which has been such a big area of escape, even in patients who have early-stage, what appears to be curable disease. This is just, I think, a very exciting time in treating this disease.

I think a cool thing is that some of these agents are going to move into the treatment of patients who don’t have HER2-positive disease, which represents a much larger group of patients, so that’s also something we’re looking forward to.

REFERENCES


INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:

- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

RET-rearranged during transfection.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-medullary thyroid cancer (non-MTC)),* and advanced or metastatic RET-mutant MTC†

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
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<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt; (95% CI: 70.9, 94)</td>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt; (95% CI: 54.7, 73)</td>
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<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> not yet reached (95% CI: 12.7, NE); median follow-up: 7.4 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td><strong>Median DoR</strong> was 17.5 months (95% CI: 12.7, NE); median follow-up: 12.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
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<tr>
<td>Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases&lt;sup&gt;1,11&lt;/sup&gt;</td>
<td>CNS DoR was ≥6 months in all responders with measurable brain metastases&lt;sup&gt;1,11&lt;/sup&gt;</td>
</tr>
<tr>
<td>No patients received radiation therapy to the brain within 2 months prior to study entry&lt;sup&gt;1,11&lt;/sup&gt;</td>
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**Advanced or Metastatic RET Fusion-Positive Thyroid Cancer (Non-MTC)**

<table>
<thead>
<tr>
<th>Systemic therapy naive&lt;sup&gt;1&lt;/sup&gt; (n=8)</th>
<th>Previously treated&lt;sup&gt;1&lt;/sup&gt; (n=19)</th>
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<tr>
<td><strong>100% ORR</strong>&lt;sup&gt;1&lt;/sup&gt; (95% CI: 63.1, 100)</td>
<td><strong>79% ORR</strong>&lt;sup&gt;1&lt;/sup&gt; (95% CI: 54.9, 94)</td>
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<tr>
<td>12.5% CR + 88% PR</td>
<td>5.3% CR + 74% PR</td>
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<tr>
<td><strong>Median DoR</strong> not yet reached (95% CI: NE, NE); median follow-up: 8.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td><strong>Median DoR</strong> was 18.4 months (95% CI: 76.5, NE); median follow-up: 17.5 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
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**Advanced or Metastatic RET-Mutant MTC**

<table>
<thead>
<tr>
<th>Cabozantinib/vandetanib treatment naive (n=88)</th>
<th>Previously treated with cabozantinib and/or vandetanib (n=55)</th>
</tr>
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<tbody>
<tr>
<td><strong>73% ORR</strong>&lt;sup&gt;1&lt;/sup&gt; (95% CI: 62.8, 82)</td>
<td><strong>69% ORR</strong>&lt;sup&gt;1&lt;/sup&gt; (95% CI: 55.8, 81)</td>
</tr>
<tr>
<td>11% CR + 61% PR</td>
<td>9% CR + 60% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> was 22.0 months (95% CI: NE, NE); median follow-up: 7.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td><strong>Median DoR</strong> not yet reached (95% CI: 19.1, NE); median follow-up: 14.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
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</tbody>
</table>

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

**Trial Design** The phase I/II, multicohort, open-label, single-arm, multicenter LIBRETTO-001 trial evaluated the efficacy of Retevmo in a population of 702 patients with metastatic RET fusion-positive NSCLC (n=332),<sup>1</sup> advanced or metastatic RET fusion-positive thyroid cancer (non-MTC)<sup>1</sup> (n=38), advanced or metastatic RET-mutant MTC (n=306), and certain other advanced solid tumors with RET alterations (n=26).<sup>4,5</sup> The study enrolled the following cohorts: systemic therapy-naive patients (n=59)<sup>1</sup> and previously treated (n=105)<sup>1</sup> patients who had progressed on platinum-based chemotherapy with metastatic RET fusion-positive NSCLC, systemic therapy-naive (n=81)<sup>1</sup> and previously treated (n=19)<sup>1</sup> patients with advanced or metastatic RET fusion-positive thyroid cancer (non-MTC), and treatment-naive (n=88)<sup>1</sup> and previously treated (n=55)<sup>1</sup> patients with advanced or metastatic RET-mutant MTC. Major efficacy outcomes were ORR and DoR. In phase II, the dose for Retevmo was 160 mg PO BID.<sup>1,10</sup> ORR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v1.1. All results reviewed by an IRC.<sup>1,3</sup>

**Adverse Reactions and Laboratory Abnormalities**

- The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.

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*Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.<sup>2</sup> Patients previously treated with platinum-based chemotherapy and with measurable CNS lesions at baseline according to IRC assessment.<sup>1</sup> Patients in this cohort received no prior systemic therapy other than radioactive iodine (RAI).<sup>3</sup> Patients in this cohort received a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI.<sup>1</sup> The efficacy of Retevmo was evaluated in 55 patients with RET-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.<sup>2</sup> Patients with advanced or metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and those without prior systemic therapy were enrolled in separate cohorts.<sup>4</sup> Non-medullary thyroid cancers (non-MTC) by histology included papillary (n=31), poorly differentiated (n=4), anaplastic (n=2), and Hurthle cell (n=1).<sup>10</sup> Other tumors included pancreatic cancer (n=7), colon cancer (n=5), and adrenal gland carcinoma (n=1).<sup>1</sup> Number of patients included in the initial efficacy analysis. Efficacy was based on patients who had at least 6 months of follow-up.<sup>1</sup> Efficacy was evaluated in 105 adult patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. All 105 patients received systemic therapy. 58 of the 105 patients received prior anti-PO-1/PD-L1 therapy, and 50 of the 105 patients received a prior multikinase inhibitor (MKI).<sup>12</sup> Patients with RET-mutant NSCLC and RET-mutant thyroid cancer (non-MTC) were not enrolled in the trial since RET is not the driver of tumor growth in these cancers.<sup>10</sup> BID=twice daily; CI=confidence interval; CNS=central nervous system; CR=complete response; Diff=duration of response; NE=not estimable; ORR=objective response rate; PO=orally; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Revevo® is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates.
Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

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

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

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

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal doses equal to or greater than the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3–4) occurring in >15% of patients who received Retevmo in LIBRETTO-001 were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspepsia (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

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

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

Laboratory abnormalities (all grades; Grade 3–4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001 were AST increased (51%; 6%), ALT increased (45%; 9%), increased total cholesterol (31%; 0.1%), increased sodium (27%; 7%), increased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2%), and decreased glucose (22%; 0.7%).

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

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

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

Concomitant use of Retevmo with CYP2C8 and CYP3A substrates increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

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

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [Clcr] <30 mL/min, estimated by Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease.

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

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

RETEVMO™ (selpercatinib) capsules, for oral use
Initial U.S. Approval: 2020

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

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

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion-positive thyroid cancer who require systemic therapy are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity.

QT Interval Prolongation
RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea, Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A4 inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

RETEVMO™ (selpercatinib) capsules, for oral use

RISK OF IMPAIRED WOUND HEALING

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on data from animal reproduction studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately 25 times greater than those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final dose.

ADVERSE REACTIONS

Clinical Trial Experience

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

RETEVMO can cause concentration-dependent QT interval prolongation.

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

<table>
<thead>
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<th>RETEVMO (n=702)</th>
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<tr>
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Table 1 summarizes the adverse reactions in LIBRETTO-001.

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

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<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (m=702)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>2'</td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
<td>0.3'</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>0.7'</td>
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<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>1.4'</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>2.3'</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
<td>4'</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
<td>1.9'</td>
</tr>
</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

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

Strong and Moderate CYP3A Inhibitors

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

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations, which may reduce RETEVOM anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETevmo is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval

RETevmo is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the final dose.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2'</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
<td>0.7'</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
<td>3.8'</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.0'</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>2.3'</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
<td>0.1'</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
<td>0.6'</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
<td>1.2'</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0'</td>
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<tr>
<td>Decreased glucose</td>
<td>22</td>
<td>0.7'</td>
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<tr>
<td>Hematology</td>
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<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6'</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7'</td>
</tr>
</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.
Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RETEVMO.

Contraception

Females

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

Males

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

Infertility

RETEVMO may impair fertility in females and males of reproductive potential.

Pediatric Use

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

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications.

Animal Toxicity Data

In 4-week general toxicology studies in rats, animals showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures > approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had localized edema of the neck and thorax.

Geriatric Use

Of 702 patients who received RETEVMO, 34% (239 patients) were >65 years of age and 10% (67 patients) were >75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were >65 years of age and younger patients.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] >30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr <30 mL/min) or end-stage renal disease.

Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

Rx only.

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

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Ki-67 Is Poised to Advance as a Biomarker in Early-Stage Breast Cancer

by JANE DE LARTIGUE, PhD

ALTHOUGH KI-67 IS A commonly used measure of cellular proliferation in breast cancer tissue, its utility as a biomarker for helping to guide therapy decisions has been clouded by technical and clinical questions. However, recent efforts to develop a framework for analyzing Ki-67 and data from several clinical trials suggest the biomarker may play a more extensive role in breast cancer treatment in the future.

Despite a lack of support for the practice from national oncology guidelines, clinicians have made wide use of Ki-67 staining with immunohistochemistry (IHC) as a prognostic biomarker in breast cancer.1 In December 2020, the International Ki-67 in Breast Cancer Working Group (IKWG) set forth recommendations for establishing analytical validity for IHC evaluation for measuring Ki-67. But the panel of breast cancer experts said that evidence for Ki-67’s clinical utility is limited to its being a prognostic biomarker, with specified cutoffs, to determine whether patients with early-stage estrogen receptor (ER)-positive disease should receive adjuvant chemotherapy.2

Although Ki-67’s recommended clinical utility does not extend beyond this specific setting, recent data from several clinical trials indicate significant promise regarding its potential for guiding therapeutic decisions.

The ADAPT trial (NCT01779206), featured in several presentations at the 2020 San Antonio Breast Cancer Symposium (SABCS 2020), bolstered evidence that, after a short course of neoadjuvant endocrine therapy (NET), an on-treatment Ki-67 index can identify patients who can be spared intensive chemotherapy in the adjuvant setting.3,4

Meanwhile, the monarchE trial (NCT03155997) was the first to prospectively investigate Ki-67 as a biomarker in a phase 3 trial of cyclin-dependent kinase inhibitors (CDKIs) in the adjuvant setting. Data reported at SABCS 2020 suggested that high Ki-67 levels in conjunction with high-risk features could be used to select patients who would benefit from the addition of abemaciclib (Verzenio) to endocrine therapy (ET) in the adjuvant treatment of ER-positive, HER2-negative stage I or II breast cancer.5

MEASURING KI-67

Unchecked proliferation is a hallmark of cancer cells,6 but not all tumors grow at the same rate; the spectrum ranges from indolent to aggressive. The ability to determine the proliferation rate could provide important information about a patient’s prognosis and even guide therapeutic decisions.

Among several methods for assessing cancer cell proliferation, Ki-67 assessment is probably the best known.2 A monoclonal antibody is used for IHC staining of the proliferation-associated nuclear protein Ki-67 in tumor cells to determine the percentage of Ki-67-positive cells among the total population of tumor cells in formalin-fixed paraffin-embedded sections obtained from a core-cut biopsy sample; this is the Ki-67 index.2,7,8

Tumors are classified as having a high or low Ki-67 index based on a prespecified cutoff. Tumors with a high Ki-67 index have a larger number of proliferating cells and are therefore likely to grow more quickly.

The Ki-67 index has a well-established role in the grading of neuroendocrine tumors9 and a variety of other cancer types, including bladder, prostate, and liver cancer; soft tissue sarcomas; and meningiomas10-15; however, these uses are much less well defined.

PROGNOSTIC MARKER

Most notably, the Ki-67 index has growing importance in breast cancer. This highly heterogeneous disease is characterized by the presence of discrete molecular subtypes with distinct clinical behaviors that can be classified according to gene expression signatures.16

Findings from numerous studies have demonstrated the prognostic value of measuring Ki-67 in breast cancers.17 In one of the largest retrospective studies, in which investigators analyzed data from a regional population-based cancer registry (N = 3568), the Ki-67 index was a prognostic factor for both disease-free survival (DFS) and overall survival (OS).

In patients with a Ki-67 index of 15% or less, 5-year DFS and OS rates were 86.7% and 89.3%, respectively, compared with 75.8% and 82.8% in patients with a high Ki-67 index (> 45%).1

The vast majority of breast cancers are ER positive and can be classified into 2 of the aforementioned molecular subtypes: luminal A and luminal B. Compared with their luminal B counterparts, luminal A tumors generally are lower grade, have higher expression of estrogen-related genes, have a better prognosis, and are more sensitive to ET.18

Distinguishing between these 2 subtypes can guide decisions about the need for added...
chemotherapy. Because the cost of gene expression analysis has limited its adoption in clinical practice, protein expression levels of ER, progesterone receptor (PR), and HER2 (determined by IHC analysis) can be used as surrogate markers for subtype classification. For ER-positive, HER2-negative breast cancers, Ki-67 has emerged as another important surrogate marker because luminal A tumors typically have a lower rate of proliferation than luminal B tumors.

The Ki-67 index was shown to discriminate between the luminal A and luminal B subtypes most effectively when a cutoff of 14% was used. This finding resulted in the 14% cutoff being adopted by the experts at the St Gallen International Breast Cancer Conference in 2011. In 2013, the majority of the St Gallen panel voted to change this threshold to 20% or greater.

This highlights a major issue that has hampered the clinical adoption of the Ki-67 index: a multiplicity of assays and lack of standardization in analysis and established cutoffs. To date, neither the American Society of Clinical Oncology nor the National Comprehensive Cancer Network clinical guidelines on breast cancer recommend using the Ki-67 index because of these issues.

The IKWG was established in 2011 to develop internationally acceptable standards relating to Ki-67 measurement. Recently updated recommendations from the group detailed a standardized visual scoring method that should be adopted, stressing the importance of quality assurance and quality control programs to maintain the analytical validity of the assay.

Among the controversies surrounding the Ki-67 assay are the multiple counting methods. The IKWG has endorsed global

**The Network**

**Ki-67 and the Cell Cycle**

**KI-67, A NUCLEAR PROTEIN**, was first discovered in the 1980s by investigators trying to generate cancer-specific monoclonal antibodies by injecting mice with nuclear preparations from Hodgkin lymphoma cells.

Since then, Ki-67 has become renowned as a marker of cell proliferation because it is expressed across the active phases of the cell cycle but is strongly downregulated in quiescent, noncycling cells. Thus, Ki-67 protein levels are higher in proliferating cells.

Ki-67 levels are not binary; rather, they represent a spectrum across the different phases of the cell cycle. Findings have even demonstrated that Ki-67 levels in quiescent cells, despite being low, can vary as a function of how long the cell has spent in a quiescent state.

The cellular function of Ki-67 is poorly understood. Although Ki-67 levels are tightly correlated with the proliferative state of the cell, it is unclear whether this protein plays a direct role in proliferation. Levels of Ki-67 are low during the G1 phase and gradually increase across S and G2 phases to reach a peak during early mitosis, with a subsequent sharp decline during anaphase and telophase (FIGURE).

In addition to its expression, the localization of the Ki-67 protein also varies over the course of the cell cycle; during interphase, it is found in the nucleoli, whereas during mitosis, after the nuclear envelope has broken down, it is found in the perichromosomal layer (PCL), a protective sheath surrounding the newly condensed chromosomes. Study results have suggested that Ki-67 is an essential component of the PCL and may help to prevent the mitotic chromosomes from collapsing back into a mass of chromatin.

Several clues as to the potential functions of Ki-67 can also be found within its structure. The Ki-67 protein contains a protein phosphatase 1 (PP1)-binding domain; PP1 is a serine/threonine phosphatase that plays an important role in mitotic exit. The protein also contains an N-terminal forkhead-associated domain, through which it interacts with phosphorylated proteins such as KIF15, a kinesin-like motor protein that helps maintain the stability of the mitotic spindle.

Ki-67 levels are regulated during the cell cycle by opposing mechanisms that control the protein’s synthesis and degradation. Ki-67 is encoded by the MKI67 gene, and its promoter contains binding sites for the E2F family of transcription factors.

The cyclin-dependent kinases CDK4 and CDK6 play an important role in the transition from G1 to S phase by phosphorylating and inactivating the retinoblastoma (Rb) protein, releasing the E2F transcription factors from repression. Thus, activation of these transcription factors allows increased MKI67 gene expression at this point in the cell cycle. At the end of mitosis, Ki-67 undergoes proteasomal degradation, which is regulated by the anaphase-promoting complex APC, an E3 ubiquitin ligase.

For a full list of references, see the article at OncLive.com.
(average) counting as opposed to “hot spot” counting, in which only the areas of highest proliferative activity are counted, as the latter has been associated with higher variability.²

The IKWG concluded that the clinical utility of Ki-67 as a prognostic marker was “evident only for prognosis estimation in anatomically favorable ER-positive and HER2-negative patients, to identify those who do not need adjuvant chemotherapy.”³

The group’s consensus was that Ki-67 levels of 5% or below or 30% or greater could be used to estimate prognosis and determine the advisability of adjuvant chemotherapy. For tumors with a Ki-67 index between these values, the group recommended using a commercially available multigene expression panel.⁴

**ENDOCRINE THERAPY TRIAGE**

Neoadjuvant chemotherapy (NAC) has become standard of care in the treatment of early-stage breast cancer because it promotes achievement of pathological complete response (pCR), which correlates with favorable long-term clinical outcomes.²⁶ Hormone receptor-positive, HER2-negative breast cancers were far less likely to exhibit a pCR to preoperative chemotherapy;²⁶ however, some patients may be offered NET alone.²⁴

Several studies have looked at baseline levels of Ki-67 as a biomarker for NET and found conflicting results. Results from IMPACT, a relatively small study (N = 330) conducted at oncology centers in the United Kingdom and Germany, showed that the baseline Ki-67 level did not significantly predict outcome following NET.²⁷,²⁸ More recently, however, investigators from the POETIC trial (NCT02338310), which was conducted in a much larger patient population (N = 4480) and used the IKWG standardized assay, reported that patients with a low baseline Ki-67 index had a lower risk of recurrence and could likely skip NET.²⁹

Although the role of baseline Ki-67 is unclear, these studies have highlighted the powerful potential of the on-treatment Ki-67 index to predict responsiveness to ET and guide decisions about subsequent adjuvant ET. The Ki-67 index at 2 to 4 weeks after starting NET indicates the level of persistent cell proliferation and resistance or response to ET and is significantly associated with risk of recurrence.²⁷,²⁹

In the POETIC trial, for patients with high Ki-67 levels at baseline and after 2 weeks of NET, the 5-year absolute risk of recurrence was 21.5%. The risk was 8.4% for those with high baseline but low 2-week Ki-67 levels, and 4.3% for those with low levels at both time points.²⁹

This idea of using on-treatment Ki-67, alongside other features that predict risk, to triage patients and avoid unnecessary chemotherapy is being prospectively evaluated in several trials. In the phase 2/3 umbrella trial ADAPT, patients underwent 3 weeks of NET and, based on their Oncotype DX Recurrence Score (RS) and Ki-67 index, were assigned to...
subsequent adjuvant ET or dose-dense NAC followed by adjuvant ET. The Oncotype DX Breast RS test is a multigene assay that assesses the expression of 16 genes associated with breast cancer, including those encoding ER, PR, HER2, and Ki-67, in addition to 5 reference genes, to generate an RS ranging from 0 to 100 that indicates the risk of cancer recurrence. Patients with high-risk disease (n = 864; defined as cN2-3 disease; grade 3 disease with post-ET Ki-67 > 40%; cN0-1 disease with RS > 25; or RS 12-25 with post-ET Ki-67 > 10%) were treated with NAC. The probability of achieving pCR was low for patients with RS of 25 or less and no response to NET (7.2% pCR), and for those with an RS greater than 25 and a response to NET (5.6% pCR). Patients with cN1 disease and an RS of 0 to 11 and those with RS 12 to 25 and a response to NET skipped NAC and were treated with adjuvant ET alone. Rates of 5-year invasive DFS (iDFS), OS, and distant DFS were 92.6%, 97.3%, and 95.6%, respectively, in the first group and 93.9%, 98%, and 96.3% in the second group. These data demonstrate that the on-treatment Ki-67 index complements the Oncotype DX RS in selecting patients for whom chemotherapy can be omitted.

In the phase 3 ALTERNATE trial (NCT01953588), patients (N = 1362) were treated with 4 to 12 weeks of NET. Investigators recommended that those with a Ki-67 index greater than 10% at week 4 or 12 (n = 286) switch to NAC. Meanwhile, endocrine responsiveness was evaluated using the modified Preoperative Endocrine Prognostic Index (mPEPI), which incorporates tumor size, number of involved lymph nodes, and on-treatment Ki-67 index. Patients with an mPEPI score of 0 (pT1-2, pN0, Ki-67 < 2.7%) received adjuvant ET, whereas those with an mPEPI score above 0 received chemotherapy and ET.

An mPEPI score of 0 has been shown to be associated with low risk of recurrence without adjuvant chemotherapy. The ALTERNATE trial is looking to prospectively validate this biomarker, and results are eagerly awaited.

An analysis of patients with a high on-treatment Ki-67 index who receive NAC in this trial was recently presented at SABCS 2020. The results indicated that salvage treatment led to very low pCR rates, suggesting that alternative treatment options will be needed for these patients.

**ADDDING CDK INHIBITORS**

To help overcome resistance to ET in breast cancer, which occurs almost universally, a number of combination strategies have been explored. Several CDKIs are FDA approved for use in combination with ET for the treatment of advanced/metastatic ER-positive, HER2-negative disease, and these successes have prompted the evaluation of this therapeutic approach in early-stage breast cancer. Investigators are also exploring whether the Ki-67 index can select patients who might benefit from the addition of a CDKI in this setting.

In the ongoing monarchE trial, 5637 patients with high-risk, node-positive, ER-positive, HER2-negative breast cancer are randomized to receive 5 to 10 years of adjuvant ET, with or without the addition of 2 years of the CDKI abemaciclib. Patients were enrolled in 2 cohorts according to clinicopathologic risk factors (cohort 1) or Ki-67 index (cohort 2).

In an exploratory subanalysis of cohort 1, the addition of abemaciclib to ET reduced the risk of iDFS by 35.7% compared with ET alone in patients with a high baseline Ki-67 index (≥ 20%). Although patients with a low Ki-67 index (< 20%) also benefited from the addition of abemaciclib, the magnitude of treatment benefit was numerically lower.

Investigators are also examining the combination of a CDKI and NET, and in several recent clinical trials, a change in the Ki-67 index from baseline after therapy served as a primary end point. The addition of a CDKI resulted in greater suppression of Ki-67 levels in the MONALEESA-1 (NCT01919229), neoMONARCH (NCT02441946), and PALLETT (NCT02296801) trials. Whether this corresponds to improved response rates, and thus whether Ki-67 levels could serve as a surrogate marker of response in this setting, remain to be determined.

Jane de Lartigue, PhD, is a freelance medical writer and editor based in Gainesville, Florida. For a full list of references, see the article at OncLive.com.
Clinical Factors Drive Choice of CDK4/6 Inhibitors for Hormone Receptor–Positive Breast Cancer

by CHRISTINA T. LOGUIDICE

During a recent OncLive Peer Exchange®, a panel of breast cancer experts examined molecular testing approaches and prognostic factors for patients with hormone receptor–positive metastatic breast cancer (mBC). Additionally, the panel put into context the clinical trial data for CDK4/6 inhibitors in this patient population, including how safety considerations may best determine the course of treatment, as well as whether the coronavirus disease 2019 (COVID-19) pandemic is impacting their prescribing practices.

UNRAVELING TUMOR BIOLOGY: WHEN AND HOW TO TEST

Since molecular testing is taking on increasing importance across many solid tumors, including breast cancer, moderator Sara A. Hurvitz, MD, asked the participants about their approach to testing in patients with advanced hormone receptor–positive breast cancer, especially as targeted treatments and the genomic data regarding them rapidly evolve.

“Besides considering patients for clinical trials in the first-line setting of novel agents like PI3K inhibitors, all I really need to know to treat patients are ER [estrogen receptor], PR [progesterone receptor], and HER2 status,” Andrew D. Seidman, MD, said. Although germline testing for BRCA mutations may be considered because it can open the door to subsequent use of PARP inhibitors, Seidman said it is not a priority in the first-line setting.

Cristofanilli described a similar approach. “In de novo metastatic breast cancer, there is no mechanism of resistance that we’re going to target upfront,” he said. In contrast, once there is recurrence, it is important to determine the drivers of resistance, he explained. “When we biopsy in the metastatic setting, if there is tissue available from additional sites, we send those for genomc
testing and NGS [next-generation sequencing] to find out if there are, for example, ESR1 mutations or [other] actionable mutations,” he said. “If there is bone disease, we can repeat NGS, so we probably look at liquid biopsies and wait to understand the molecular drivers for these patients,” he explained. He remarked that this approach helps identify which endocrine therapy backbone is most likely to benefit each individual patient. “We may even find F2 mutations that are actionable at this point. There are data suggesting these patients respond to tyrosine kinase inhibitors [TKIs] for HER2 [targeting]. But it’s very important to rule out immediately if an ESR1 mutation is the driver of the resistance,” he said.

Hurvitz added that there is no consensus on when to conduct molecular testing in patients with de novo hormone receptor-positive mBC. “Some people wait until the second- or third-line setting,” she said. “Certainly, for clinical trials, many of us are interested in querying what the tumor biology is for clinical trial eligibility.”

UNDERSTANDING PROGNOSTIC FACTORS

The discussion turned to prognostic factors in hormone receptor-positive mBC. Sara Tolaney, MD, MPH, said that when assessing disease prognosis for patients who have either recurrent or de novo disease in the first-line setting, physicians should consider the disease-free interval. “We know that patients who are recurrent on their endocrine therapy—particularly early on in their endocrine treatment, usually within the first 2 years of adjuvant therapy—are patients with endocrine-refractory disease. These are patients who we know are not going to be as sensitive to future endocrine therapy and generally have a poor prognosis. Someone who recurs 10 or 15 years later or who has de novo disease—those are patients with very different biology in their tumor and [they] generally have better prognostic features,” she explained.

Another important prognostic consideration Tolaney noted is the site of disease. She explained that significant visceral involvement, especially liver involvement, is associated with a worse prognosis compared with bone metastases. Other poor prognostic factors include presence of higher-grade tumors and PR negativity. Some molecular tests may also help give an indication of prognosis, such as those evaluating circulating tumor cells (CTCs), she said, and noted that Cristofanilli has done considerable work in this area. For example, in an international expert consensus paper coauthored by Cristofanilli in 2019, CTC enumeration was demonstrated to be prognostic independent of clinical and molecular variables. Data from the study showed that patients with at least 5 CTCs/7.5 mL had a more aggressive disease course, whereas those with fewer than 5 CTCs/7.5 mL were found to have a more indolent disease course. In patients with hormone receptor-positive disease, this translated to a 26-month or higher OS benefit in the indolent group (44.0 vs 17.3 months; P < .0001).

EXAMINING THE SAFETY AND EFFICACY OF CDK4/6 INHIBITORS

CDKs are multifunctional enzymes that play an important role in regulating the cell cycle. CDK4/6 inhibitors block cell-cycle progression during the G1 phase of the cell cycle, thereby preventing cancer progression. In patients with hormone receptor-positive, HER2-negative breast cancer, CDK4/6 inhibitors are currently a National Comprehensive Cancer Network (NCCN) preferred first-line therapy in combination with aromatase inhibitors (AIs). They are also a preferred second- and subsequent-line treatment in combination with fulvestrant (Faslodex) in patients who have not previously received a CDK4/6 inhibitor. Although it is possible that the 3 FDA-approved agents (ie, palbociclib, ribociclib, abemaciclib) have similar efficacy, the panelists mentioned some key distinctions in the study populations in which these agents were studied, suggesting there may be some differences in benefit between agents.

“There are some studies where the patients were endocrine resistant. Some others included patients with de novo disease who had not been exposed to prior endocrine therapy,” Cristofanilli said, noting that sites of metastasis also varied between studies. “It seems that some of the agents would be more effective in those with endocrine resistance or visceral metastases, whereas others are particularly effective in patients with endocrine sensitivity and bone disease,” he said. Cristofanilli added that these distinctions between studies make it difficult to determine if efficacy is a function of the agents themselves or if it is characteristic of the patients enrolled in these studies. Nevertheless, he emphasized the importance of considering such distinctions when deciding between CDK4/6 inhibitors in clinical practice.

Another important consideration is the varied toxicity profiles of these agents (TABLE). According to the participants, many toxicities that initially seemed difficult to manage have become less intimidating, such as neutropenia, which is a common adverse effect (AE) investigators observed across all 3 CDK4/6 inhibitors. “We feel pretty comfortable knowing how to manage that now by checking CBC [complete blood
count] twice weekly in the first 2 months, perhaps at the first day of a couple of cycles, then based on discretion afterward. The same applies for potential liver function abnormalities,” Seidman said.

**Palbociclib**
Investigators of the PALOMA-2 study (NCT01740427) assessed palbociclib plus letrozole (Femara) versus placebo plus letrozole in 666 treatment-naïve postmenopausal women with hormone receptor–positive, HER2-negative mBC. After a median follow-up of 23 months, the study showed a PFS of 24.8 months in the palbociclib arm compared with 14.5 months in the placebo arm (HR, 0.58; 95% CI, 0.46-0.72; P < .001). With extended follow-up of approximately 38 months, the PFS benefit increased further with the addition of palbociclib, reaching 27.6 months. PFS remained unchanged for patients treated with placebo plus letrozole (HR, 0.563; 95% CI, 0.461-0.687; P < .001).

“We’re still waiting for PALOMA-2 to read out in terms of survival,” Cristofanilli said. OS is generally considered the most important end point in clinical trials, but Seidman pointed out that “PFS still has primacy in the first-line setting for estrogen receptor–positive, HER2-negative disease.”

In the PALOMA-3 study (NCT01942135), which assessed palbociclib plus fulvestrant versus placebo plus fulvestrant in the second-line setting, the addition of the CDK4/6 inhibitor resulted in an almost 7-month longer median OS after 44.8 months of follow-up in 521 women who relapsed or progressed on endocrine therapy.11 The median OS was 34.9 months with palbociclib plus fulvestrant compared with 28.0 months with placebo plus fulvestrant (HR for death, 0.81; 95% CI, 0.64-1.03; P = .09), but the finding did not reach statistical significance. When considering the subset of patients with sensitivity to previous endocrine therapy (n = 410), the median OS was 39.7 months in the palbociclib arm and 29.7 months in the placebo arm, showing an absolute difference of 10 months (HR, 0.72; 95% CI, 0.55-0.94).11

“If in the first line you have de novo and bone-only disease, there’s no question that using palbociclib in combination with an AI is absolutely a reasonable choice,” Cristofanilli said. The agent may be considered for patients with visceral disease, having shown a PFS benefit over placebo plus an AI and placebo plus fulvestrant combinations; nevertheless, a [different] CDK4/6 inhibitor may be better for such patients based on available data. For example, some data suggest the benefit of palbociclib is reduced in patients with visceral disease compared with those without. Specifically, in the second-line setting, the median OS was 27.6 months among the 311 patients with visceral metastatic disease treated with palbociclib plus fulvestrant versus 46.9 months in the 210 patients without visceral metastatic disease who were treated with this combination.11

**Ribociclib**
Ribociclib has been assessed in various combinations and populations in the first- and second-line settings. In MONALEESA-2 (NCT01958021), investigators evaluated first-line ribociclib plus letrozole compared with placebo plus letrozole in 668 postmenopausal women, with a median follow-up of 26.4 months. Findings showed a 9.3-month PFS benefit in the ribociclib arm (25.3 vs 16.0 months; HR, 0.568; 95% CI, 0.457-0.704; log-rank P = 9.63 x 10⁻⁹). The OS data were

**CLINICAL IMPLICATIONS**

**Overall Survival Data Build for CDK4/6 Inhibitors**
Recent clinical trial findings add overall survival (OS) data to positive outcomes for CDK4/6 inhibitors in patients with hormone receptor–positive, HER2-negative breast cancer.

**Palbociclib (Ibrance)**
- **PALOMA-3 (NCT01942135):** Palbociclib plus fulvestrant (Faslodex) in second-line setting in pre-, peri-, or postmenopausal women
  - The median OS after a median follow-up of 44.8 months was 34.9 months (95% CI, 28.8-40.0) with palbociclib combination vs 28.0 months (95% CI, 23.6-34.6) with fulvestrant plus placebo (HR for death, 0.81; 95% CI, 0.64-1.03; P = .09).

**Ribociclib (Kisqali)**
- **MONALEESA-3 (NCT02422615):** Ribociclib plus fulvestrant as first- or second-line treatment for postmenopausal women
  - The estimated OS rate after a median follow-up of 39.4 months was 57.8% (95% CI, 52.0%-63.2%) for ribociclib arm vs 45.9% (95% CI, 36.9%-54.5%) for placebo plus fulvestrant (HR for death, 0.72; 95% CI, 0.57-0.92; P = .00455).
- **MONALEESA-7 (NCT02278120):** Ribociclib plus endocrine therapy and goserelin in peri- and premenopausal women
  - The estimated OS rate at 42 months was 70.2% (95% CI, 63.5%-76.0%) for the ribociclib arm and 46.0% (95% CI, 32.0%-58.9%) for placebo plus endocrine therapy and goserelin (HR for death, 0.71; 95% CI, 0.54-0.95; P = .00973 by log-rank test).

**Abemaciclib (Verzenio)**
- **MONARCH 2 study (NCT02107703):** Abemaciclib plus fulvestrant as second-line therapy for pre-, peri-, or postmenopausal women
  - The median OS benefit after a median follow-up of 47.7 months was 46.7 months in the abemaciclib arm vs 37.3 month for placebo plus fulvestrant (HR, 0.757; 95% CI, 0.606-0.945; P = .01).
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U.S. News & World Report has recognized Hackensack Meridian John Theurer Cancer Center at Hackensack University Medical Center as the best cancer center in all of New Jersey. And as a member of one of just 16 NCI-designated cancer consortia, we have distinguished ourselves as New Jersey’s premier cancer center—offering nationally recognized cancer specialists, clinical trials and immunotherapy including CAR T-Cell.

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
still immature, but 50 deaths in the ribociclib arm and 66 in the placebo arm had occurred. MONALEESA-3 (NCT02422615) included treatment-naïve postmenopausal women as well as postmenopausal women who had received up to 1 line of endocrine therapy in the advanced setting. Investigators randomized patients 2:1 to either ribociclib plus fulvestrant (n = 484) or placebo plus fulvestrant (n = 242). Both treatment-naïve and previously treated women showed benefit with the addition of ribociclib, with a median PFS of 15 months in the ribociclib arm compared with 12 months in the placebo arm. The estimated OS rates were 70.2% and 43.5% at 36 months, respectively; HR, 0.57-0.92; P = .00455). With an extended follow-up of 42 months, treatment-naïve patients had a PFS of 33.6 months in the ribociclib arm compared with 19.2 months in the placebo arm. The addition of ribociclib also showed significant OS benefit, with a 28% difference in the relative risk of death, which was consistent across most subgroups. The estimated OS rate was 57.8% for ribociclib versus 45.9% for placebo (HR, 0.72; 95% CI, 0.57-0.92; P = .00002). Folong-up to 47.7 months showed a significant PFS benefit with the addition of abemaciclib, with a median PFS of 16.9 months in the abemaciclib arm versus 9.3 months in the placebo arm (HR, 0.536; 95% CI, 0.445-0.645). Additionally, investigators observed an OS benefit in the abemaciclib arm (46.7 vs 37.3 months, respectively; HR, 0.757; 95% CI, 0.606-0.945; P = .01).

If you have a [patient with] primary resistant disease, maybe with visceral metastases or liver disease, abemaciclib is something that may make them more comfortable,” Cristofanilli said. A challenge with abemaciclib is that it has a higher risk of gastrointestinal toxicity than the other CDK4/6 inhibitors. However, these toxicities can be managed. “With experience, time, and the use of antimiility agents, physicians have become comfortable using this agent,” he said. Cristofanilli also explained that in MONARCH-3 the likelihood of discontinuing abemaciclib because of diarrhea was low. In the final PFS analysis of the trial, only 6 abemaciclib-treated patients (1.8%) discontinued treatment because of diarrhea. Most cases of diarrhea (72.8%) were low grade, occurred early in the treatment course (69.1%), and were successfully managed with antidiarrheal medications and dose adjustments.

**TREATMENT CONSIDERATIONS DURING COVID-19**

A concern with CDK4/6 inhibitors is that they may increase patients’ susceptibility to and the severity of COVID-19 because the inhibitors are associated with decreased neutrophil counts. Findings from a small study presented during the 2020 American Association for Cancer Research Virtual Meeting: COVID-19 and Cancer suggested that withdrawal or dose reduction of these agents may reduce the incidence of COVID-19; however, the findings did not reach statistical significance and the investigators noted a need for higher-quality data. In the MONARCH 2 study (NCT02107703) compared abemaciclib plus fulvestrant with placebo plus fulvestrant as a second-line treatment for 669 pre-, peri-, or postmenopausal women who had progressed on endocrine therapy. Follow-up to 47.7 months showed a significant PFS benefit with the addition of abemaciclib, with a median PFS of 16.9 months in the abemaciclib arm versus 9.3 months in the placebo arm (HR, 0.536; 95% CI, 0.445-0.645). Additionally, investigators observed an OS benefit in the abemaciclib arm (46.7 vs 37.3 months, respectively; HR, 0.757; 95% CI, 0.606-0.945; P = .01).
Pediatric Leukemia Pioneer
Emil J. Freireich Dies at 93
by JASON HARRIS

EMIL J. FREIREICH, MD, DSC, a founding father of modern clinical cancer research and the 2015 Giants of Cancer Care® award winner for advances in lymphoid neoplasms, died February 1, 2021, at The University of Texas MD Anderson Cancer Center in Houston, where he was a faculty member for 50 years. He was 93 years old.

Dr Freireich was known for his confidence, passion, and occasional ferocity. He was fired 8 times during his career, and his friends were amazed that number wasn’t higher. Bart Barlogie, MD, one of Dr Freireich’s protégés and the 2018 Giants of Cancer Care® award winner in the multiple myeloma category, believes that for all the honors Dr Freireich received during career, his mentor deserves even greater recognition for his achievements.

“If they gave the Nobel Prize in medicine for clinical advancements, rather than purely scientific discoveries, Emil J. Freireich—who’s known to friends as Jay—would have been one of at least 3 different prize-winning teams for the work he did at the NCI [National Cancer Institute],” Barlogie said in a 2015 interview. “The thing is, his run did not end there. After he jumped to MD Anderson in 1965, he put together a team that leveraged his insights in combination chemotherapy and other areas to create treatments that have become curative for many other cancers.”

Dr Freireich is credited as the originator of combination chemotherapy for acute lymphoblastic leukemia (ALL), the primary architect of the first cure for a systemic cancer, and a major contributor to curative therapies for a half-dozen other cancers. Early in his career, he helped invent a device that separates blood products to alleviate the uncontrolled bleeding common to patients with ALL, the most common childhood leukemia.

He played a key role in transforming MD Anderson from a minor facility to one of the world’s leading cancer centers. Dr Freireich worked at MD Anderson from 1965 to 2015 and led the Leukemia Research Program there for decades. In 2005, the cancer center established the Emil J. Freireich Award for Excellence in Education in recognition of his teaching contributions as a founding member of The University of Texas System Academy of Health Science Education.

“Dr Freireich was a giant of modern medicine whose impact on the field of cancer is beyond compare. His passing will be felt around the world and within the MD Anderson community,” Peter WT Pisters, MD, president of MD Anderson, said in a news release. “For more than 60 years, he pushed boundaries and devoted himself to saving young lives and relieving suffering. Dr Freireich’s compassion and empathy, with a focus on the holistic needs of individual patients, were fused with scientific creativity and perseverance. This rare blend of exceptional qualities has created a lasting legacy that will forever be part of the history of cancer research and that of MD Anderson.”

In 1955, Dr Freireich joined the NCI, where he was assigned to care for children with leukemia. After observing that most patients bled to death before undergoing treatment, he hypothesized that the bleeding was caused by insufficient platelets. In order to obtain enough platelets to treat patients, he developed the first continuous-flow blood cell separator.

He went on to partner with Emil “Tom” Frei III, MD; Charles Gordon Zubrod, MD; and James F. Holland, MD, the 2016 Giants of Cancer Care® award winner for hematologic malignancies, to investigate chemotherapy drug combinations to treat childhood leukemia.

In a 1961 trial, Dr Freireich and colleagues administered a 4-drug regimen comprised of vincristine, amethopterin, 6-mercaptopurine, and prednisone, now known as VAMP, to patients with ALL. The medical establishment feared the combination would be as fatal as the disease. “Instead, 90% of [the patients] went into remission,” Dr Freireich said in an interview. “It was magical.”

Today, the 5-year survival rate for children with ALL is approximately 90% overall, according to the American Cancer Society.

In 1965, MD Anderson recruited Drs Freireich and Frei to launch a chemotherapy program. They formed the Department of Developmental Therapeutics and hired scientists to investigate drug combinations that could potentially treat other cancers based on the same methods they used in ALL.

Dr Freireich went on to perform leukocyte transfusion and demonstrate engrafting of peripheral blood stem cells, providing allogeneic bone marrow grafts. Further, he developed allogeneic platelet transfusion and treatment strategies for infectious complications.

“He truly is the father of modern leukemia therapy, being the first to test leukemia drugs and to drive innovation in a disease that no one else had the courage to confront,” Hagop M. Kantarjian, MD, chair of leukemia at MD Anderson and the 2014 Giants of Cancer Care® award winner in the leukemia category, said in a news release.

Kantarjian met Freireich in 1978 as a fourth-year medical student and eventually joined him on staff. “He encouraged us to dare [to] challenge existing dogmas in cancer research. He inspired my passion to work toward cures for patients and to change the face of this disease.”

Dr Freireich is survived by his wife, Haroldine; 4 children; 6 grandchildren; and 3 great-grandchildren.

In lieu of flowers, the family would appreciate donations to MD Anderson via mdacc.convio.net/goto/Freireich.
Clonal evolution is a root cause of treatment resistance in multiple myeloma that may ultimately result in triple-class refractory (TCR) disease. Patients are considered TCR when they are resistant to ≥1 treatment in all 3 standard-of-care classes (proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies). 1-4

Peptide-drug conjugates and antibody-drug conjugates represent a strategy designed to deliver a cytotoxic agent directly into tumor cells. 5