Predominant Lung Cancer Investigator Welcomes a New Era of Research

PEER EXCHANGE®
Experts Explore Complex Landscape of Chemotherapy-Induced Neutropenia

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Novel Immunotherapy Combos Target TIM-3 and PD-1/PD-L1 Networks

16TH ANNUAL NEW YORK LUNG CANCERS SYMPOSIUM®
Experts Review 2021 Highlights in NSCLC

DRUG SPOTLIGHT
Michael J. Mauro, MD, on the Approval of Asciminib in Ph+ CML

CLINICAL TRIAL IN FOCUS
Expansion Cohort Explores Efficacy of Novel Treatment for WALDENSTRÖM MACROGLOBULINEMIA

MONTEFIORE EINSTEIN CENTER FOR CANCER CARE
By Nitin Ohri, MD, MS
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

*Study design: Phase 2 open-label, single-arm trial (N=145) to evaluate the efficacy and safety of ZYNLONTA as a monotherapy in r/r DLBCL after 2 or more systemic therapies. Patients received 0.15 mg/kg Q3W for 2 cycles with dexamethasone premedication (unless contraindicated), then 0.075 mg/kg Q3W for subsequent cycles. Primary endpoint was ORR, evaluated by independent review committee using Lugano 2014 criteria. ZYNLONTA was administered until progressive disease or unacceptable toxicity.1

**IMPORTANT SAFETY INFORMATION

**WARNINGS AND PRECAUTIONS**

**Effusion and Edema** Serious effusion and edema occurred. Grade 3 edema: 3% (primarily peripheral edema or ascites); Grade 3 pleural effusion: 3%; Grade 3/4 pericardial effusion: 1%.

Monitor patients for new/worsening edema or effusions. Withhold ZYNLONTA for Grade >2 until toxicity resolves. Consider diagnostic imaging in patients with symptoms of pleural or pericardial effusion, such as new/worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management.

**Myelosuppression** Serious or severe myelosuppression—including neutropenia, thrombocytopenia, and anemia—occurred. Grade 3/4 neutropenia: 32%; thrombocytopenia: 20%; anemia: 12%. Grade 4 neutropenia: 21%; thrombocytopenia: 7%. Febrile neutropenia occurred: 3%.

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA.

Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

**Infections** Fatal and serious infections, including opportunistic infections, occurred. Grade ≥3: 10%; fatal infections: 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Monitor for any new/worsening signs or symptoms consistent with infection. For Grade 3/4 infection, withhold ZYNLONTA until infection has resolved.

**Cutaneous Reactions** Serious cutaneous reactions occurred. Grade 3: 4%, including photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.

Monitor patients for new/worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for Grade 3 until resolution. Advise patients to: minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows; protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, consider dermatologic consultation.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.
You may also report side effects to ADC Therapeutics at 1-855-690-0340.

AR = adverse reaction; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = overall response rate; NE = not estimable; PR = partial response; r/r = relapsed or refractory
more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Challenge expectations in 3L DLBCL

Take the next step...

...on the path to response with the first and only single-agent, CD19-directed ADC\(^1,2\)

<table>
<thead>
<tr>
<th>48.3% ORR(^{a\dagger\ddagger})</th>
<th>1.3 Months</th>
<th>Single-Agent IV(^{1,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI: 39.9, 56.7)(^1)</td>
<td>median time to response</td>
<td>30-minute infusion</td>
</tr>
<tr>
<td>24.1% CR; 24.1% PR(^\ddagger)</td>
<td>(range: 1.1–8.1)(^1)</td>
<td>Once every 3 weeks</td>
</tr>
<tr>
<td>(95% CI for each: 17.4, 31.9)(^1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Median duration of response: 10.3 months (95% CI: 6.9, NE). Of 70 patients with objective response, 25 (36%) were censored prior to 3 months; 26% of responders had a DOR of ≥6 months.\(^1\)

\(^b\) Premedication: dexamethasone 4 mg (oral or IV) twice daily for 3 days, beginning the day before infusion. If dexamethasone administration does not begin the day before ZYNLONTA, it should begin at least 2 hours prior to ZYNLONTA infusion (unless contraindicated).\(^1\)

\(^\dagger\) Median follow-up time: 7.3 months (range: 0.3–20.2).\(^1\)

\(^\ddagger\) ORR: n=70. CR: n=35. PR: n=35.\(^1\)

Embryo-Fetal Toxicity ZYNLONTA can cause embryofetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

ADVERSE REACTIONS In a pooled safety population (215 patients, Phase 1 and LOTIS-2), the most common (>20%) ARs, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase (GGT), neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

In LOTIS-2, serious ARs occurred in 28% of patients. The most common (>2%) were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis.

Fatal ARs: 1%, due to infection.

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

www.zynlontahcp.com

DOSE DELAYS AND MODIFICATIONS Permanent treatment discontinuation due to an AR of ZYNLONTA: 19%. Of these, ≥2% were increased GGT, edema, and effusion.

Dose reductions due to an AR of ZYNLONTA: 8%. Of these, ≥4% was increased GGT.

Dosage interruptions due to an AR of ZYNLONTA: 49%. Of these, ≥5% were increased GGT, neutropenia, thrombocytopenia, and edema.

For Grade ≥3 nonhematologic toxicity, hold ZYNLONTA until toxicity ≤Grade 1. For neutropenia: if ANC <1 x 10^9/L, hold ZYNLONTA until ANC ≥1 x 10^9/L. For thrombocytopenia: if platelet count <50,000/mcL, hold ZYNLONTA until ≥50,000/mcL. For Grade ≥2 edema or effusion, hold ZYNLONTA until ≤Grade 1. If dosing is delayed >3 weeks due to toxicity related to ZYNLONTA, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation.

Note: If toxicity requires dose reduction following second dose of 0.15 mg/kg (C2D1), patient should receive 0.075 mg/kg for Cycle 3.
ZYNLONTA® (loncastuximab tesirine-lpyl) for injection, for intravenous use
The following is a Brief Summary; refer to full Prescribing Information for complete product information.

**INDICATIONS AND USAGE**
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

**CONTRAINDICATIONS**
None

**WARNINGS AND PRECAUTIONS**

**Effusion and Edema.** Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

**Myelosuppression.** Treatment with ZYNLONTA can cause severe or serious myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

**Infections.** Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

**Cutaneous Reactions.** Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculopapular), and erythema. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

**Embryo-Fetal Toxicity.** Based on its mechanism of action, ZYNLONTA can cause embryofetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA, and for 6 months after the last dose (see Use in Specific Populations (8.1, 8.3)).

**ADVERSE REACTIONS**

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

**Effusion and Edema**

**Myelosuppression**

**Infections**

**Cutaneous Reactions**

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADCT-402-201 (LOTIS-2) and ADCT-402-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles. In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hyperalbuminemia, rash, edema, nausea, and musculoskeletal pain.

**Relapsed or Refractory Diffuse Large B-Cell Lymphoma**

LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies (see Clinical Studies (14.1)). The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

**Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYNLONTA (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>38</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>30</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>23</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspneae</td>
<td>13</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2

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<tr>
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<th>Grades 3 or 4 (%)</th>
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<td></td>
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<tr>
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<td>1a</td>
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<td>30</td>
<td>2a</td>
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</tr>
<tr>
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<td>0</td>
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<td>3</td>
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<td>12</td>
<td>0</td>
<td></td>
</tr>
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<td></td>
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<td>23</td>
<td>1a</td>
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</tr>
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<td>Metabolism and Nutrition Disorders</td>
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</tr>
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<td>15</td>
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</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dyspneg</td>
<td>13</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
<td>2a</td>
<td></td>
</tr>
</tbody>
</table>

*Clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA included:

- Blood and lymphatic system disorders: Febrile neutropenia (3%)
- Cardiac disorders: Pericardial effusion (3%)
- Infections: *Pneumonia* (5%), *sepsis* (2%)
- Skin and subcutaneous disorders: *Hyperpigmentation* (4%)
- General disorders: Infusion site extravasation (<1%)

Selected Other Adverse Reactions

- Inflammatory-related conditions were reported in 3% of patients in LOTIS 2, including pericarditis, pneumonitis, pleuritis, and dermatitis.

Table 2 summarizes the laboratory abnormalities in LOTIS 2.

Table 2: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYNLONTA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>58</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>52</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>51</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>57</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>48</td>
</tr>
<tr>
<td>AST increased</td>
<td>41</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
</tr>
<tr>
<td>ALT increased</td>
<td>34</td>
</tr>
</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, ZYNLONTA can cause embryofetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse 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**

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-iply. The cytotoxic component of ZYNLONTA, SG3199, crosses DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

**Lactation**

**Risk Summary**

There is no data on the presence of loncastuximab tesirine-iply or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

**Females and Males of Reproductive Potential**

ZYNLONTA can cause fetal harm when administered to pregnant women.

**Pregnancy Testing**

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

**Contraception**

**Females** Advise women of reproductive potential to use effective contraception during treatment and for 9 months after the last dose.

**Males** Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 6 months after the last dose.

**Infertility**

**Males** Based on the results from animal studies, ZYNLONTA may impair fertility in males. The effects were not reversible in male cynomolgus monkeys during the 12-week drug-free period.

**Pediatric Use**

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

**Geriatric Use**

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

**Hepatic Impairment**

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).

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Predominant Lung Cancer Investigator Welcomes a New Era of Research

by ANDREW SMITH

Julie Brahmer, MD, MSc, who helped pioneer PD-1/PD-L1 immunotherapy, previews the 19th Annual Winter Lung Cancer Conference®, sharing her thoughts about major trends in the field and the future of molecular testing.

From the Physician’s Desk

35 Immunotherapy Paves Path for New Standards of Care in Gastroesophageal Cancers
By Kanak Parmar, MD; and Sarbajit Mukherjee, MD, MS

16TH ANNUAL NEW YORK LUNG CANCERS SYMPOSIUM®

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AS INVESTIGATORS REFLECT ON another year gone by, the new year promises the publication of pivotal data, approvals, and advances across tumor types. For some, reflection on the past year marks strides in their career with additional highlights added to their extensive accomplishments. For others, looking to the achievements of others represent the stepping stones that will allow them to build their own legacy and improve outcomes for patients in their respective specialty.

In our cover story this issue, one leader in thoracic oncology, Julie R. Brahmer, MD, MSc, discusses the trajectory of her career and how innovation efforts in her early days continue to fuel her desire to see her efforts through from start to finish.

“I had been the principal investigator on a lot of phase 1, first-in-human trials that just never went anywhere,” said Brahmer, who is codirector of the Upper Aerodigestive Cancer Department at Johns Hopkins Medicine’s Bloomberg~Kimmel Institute for Cancer Immunotherapy in Baltimore, Maryland. “So, even the phase 1 trial was exciting because in patients who responded well the disease would just melt away and not come back for months or years. That feeling continued among the oncology community as a whole until the phase 3 study and even at that point, a lot of [individuals] still felt it was a fluke...all these years later, seeing that there are groups of patients within lung cancer—as well as other cancers—benefitting from these treatments, it’s very exciting and gratifying...to know that I played a small part in the development of this thing that has extended so many lives among patients who did not have many treatment options until then.”

Brahmer has continued to study the use of immunotherapies in lung cancer treatment, and she and other investigators have made many discoveries over those years that have increased the benefits such medications give patients. She will lead discussions on the next wave change in thoracic oncology as part of the 19th Annual Winter Lung Cancer Conference® hosted by Physicians’ Education Resource®, (PER®), LLC.

As Brahmer reflects on the results that have laid the groundwork for her career, Meredith McKean, MD, MPH, discusses the trials that will direct the future of hers. In an interview with OncologyLive® McKean, the associate director of the Melanoma and Skin Cancer Research Program at Sarah Cannon Research Institute in Nashville, Tennessee, unpacks how research in the field is shifting and putting a focus on digging into the rare subtypes. “[Efforts] reaching out into these rarer subtypes, [such as] uveal melanoma, after having some early success with tebentafusp, and seeing several other targeted therapy trials and specific treatment options just for those patients, has been exciting to be a part of.”

As directions change and career focuses become more targeted, PER® will continue to offer the programs designed to support clinicians on their journey. For a full listing of the offerings on the docket for 2022, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences™

Publisher’s Note

A Brighter Future for Oncology Research
The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

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

To nominate, please visit: giantsofcancercare.com/nominate

PROGRAM OVERVIEW

- Nominations are open through February 28, 2022.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection Committee of more than 120 oncologists will vote to determine the 2022 inductees.
- The 2022 Giants of Cancer Care® class will be announced in Spring 2022.
The Future of Cancer Care Depends on Trust in the Scientific Community

by MAURIE MARKMAN, MD

Much has been written over the past 18 months regarding the angst associated with the fallout from the COVID-19 pandemic, including its effect on the economy, decisions to restart essential activities such as in-person schooling, and more recently mandates for vaccination. Unfortunately, but of necessity, the scientific community—particularly national, regional, and local public health officials—has found itself in the middle of much of the controversy associated with the (hopefully) optimal management of the pandemic’s negative effects. To achieve this goal, leaders at all levels of government have had to make difficult and often quite unpopular decisions.

A recent front-page article in *The New York Times* highlighted the extraordinary pressure being placed on health officials and the devastating personal attacks to which many of these individuals have been subjected as a result of efforts to do their best to protect the public. One official in Washington state, for example, was attacked online, with 1 post suggesting “bringing back public hangings” after she announced a local mask mandate. In a number of settings state lawmakers without public health experience have assumed responsibility for the functions of trained and experienced experts.

Unfortunately, the scientific community, particularly the critical national health regulatory authorities (FDA, CDC), have likely contributed to much of the confusion through less-than-optimal communication during the pandemic. Factors contributing to the uncertainty include changing recommendations with often confusing explanations regarding complex economic and political topics, and sometimes even contradicting decisions issued by various agencies or their advisors.

Further, efforts to find answers to unresolved, critically relevant questions about the actual origin of the virus responsible for the pandemic have revealed distressing conflicts of interest among members of the international scientific community. This includes concerns of whether the National Institutes of Health may have unknowingly funded research efforts in China to inappropriately, and remarkably dangerously, enhance the ability of coronaviral spread to humans. It is not unreasonable to suggest that such revelations may serve to heighten concern regarding the objectivity of scientific leaders and public health officials entrusted to protect the public’s interests.

Other concerns noted in scientific literature threaten to further erode trust but have fortunately not yet been highlighted in the mainstream lay press. Some of these concerns appear to be unique to specific regions of the world, including reports of population-based germline analysis in China conducted with woefully inadequate (or completely absent) informed consent, and organized crime charges being brought against scientists in Mexico. However, other issues may be far more relevant in the United States, including disturbing evidence that scientific misconduct is not a rare event, as identified in an anonymous survey of Dutch scientists, 8% of whom admitted to fabrication or falsification of research results within the past 3 years. The serious inadequacy of scientific peer review is another concern, with a paper published in the journal *Vaccines* inappropriately concluding that for every 3 deaths prevented by COVID-19 vaccination, we have to accept 2 inflicted by vaccination.

It is now appropriate to inquire how the preceding discussion is relevant within the oncology domain. In the opinion of this commentator, it is not unreasonable to state that a substantial percentage of the advances in cancer management over more than a decade have focused almost exclusively on the development of new antineoplastic pharmaceutical agents. There is certainly nothing wrong with this state of affairs and research in this arena should continue to be strongly encouraged; however, other factors must be acknowledged, including a rise in the aging population which is certain to correlate with a rise in the incidence of cancer and the simply unsustainable financial reality of this situation on individuals, families, and society. Further, as advanced cancers in several settings have become more chronic disease processes, the natural histories of which are increasingly measured in years rather than months, the cost of providing drug...
therapy for a far more prolonged period of time will challenge the budgets of all payers, including the government.

One critical component of a possible partial solution to this dilemma is a full-force effort in cancer prevention. Efforts should include promoting currently available vaccines (such as human papillomavirus [HPV] and hepatitis) and future vaccines, continuing major societal efforts in smoking cessation, and substantially expanding strategies to combat the raging epidemic of obesity (beginning with first-class research designed to determine how to effectively approach this issue).

One only needs to review the recent literature to understand the remarkable effect of widespread acceptance of HPV vaccination on reducing the burden of cervical cancer to appreciate the critical role that cancer prevention may play in the future in a fiscally sustainable approach to dealing with cancer. In a recent population-based report from the United Kingdom, routine vaccination for girls aged 12 to 13 years and a catch-up program for those aged 14 to 18 years was shown to reduce the risk of cervical cancer by 87% and CIN3 by 97% compared with an unvaccinated population of the same ages.⁷

Smoking cessation, including among individuals who have already developed a smoking-related malignancy, has been shown to be highly effective in preventing cancer or in certain circumstances reducing the risk of recurrence. In a study of 517 smokers with a diagnosis of early-stage (IA–IIIA) non–small cell lung cancer, the median overall survival was almost 2 years longer for individuals who discontinued smoking compared with those who continued the habit after their cancer diagnosis.⁸ Further, both cancer-specific (HR, 0.75) and all-cause mortality (HR, 0.67) was substantially improved in those able to stop smoking.

In conclusion, an important consideration is that evidence strongly supports that approaches to cancer prevention focused on vaccination of individuals who do not already have cancer, or ones that demand changes in well-established behaviors, have little chance of success unless those being targeted are willing to listen to, and ultimately trust, the recommendations being made by members of the scientific community.

REFERENCES
5. de Vries J. Large survey finds questionable research practices are common. Science. 2021;373(6552):265. doi:10.1126/science.373.6552.265
The FDA has approved pembrolizumab (Keytruda) for the adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy alone or with resection of metastatic lesions.

The approval of the PD-1 inhibitor was supported by efficacy data from the phase 3 KEYNOTE-564 trial (NCT03142334). Results from an interim analysis showed that patients who received pembrolizumab elicited a statistically significant improvement in investigator-assessed disease-free survival (DFS) compared with those who received placebo, reported at 109 events (22%) vs 151 events (30%), respectively (HR, 0.68; 95% CI, 0.53-0.87; P = .001). The median DFS had not yet been reached in either arm. However, the 24-month DFS rates were 77% (95% CI, 73%-81%) vs 68% (95% CI, 64%-72%), respectively.

At the time of the DFS analysis, overall survival data were immature and 95% of patients remained alive in the overall population (N = 994).

Ropeginterferon Alfa-2b-njft Expands Treatment Options for Polycythemia Vera

The FDA has approved ropeginterferon alfa-2b-njft (Besremi) for the treatment of patients with polycythemia vera.

The phase 1/2 PEGINVERA trial (NCT01193699) provided the data to support the efficacy findings used to support this approval; safety data contained findings from PEGINVERA and the phase 3 PROUD-PV (EudraCT 2012-005259-18) and CONTINUATION-PV (EudraCT 2014-001357-17) trials. Findings showed that among 51 patients evaluated following the 7.5 years treatment period, 61% (95% CI, 46%-74%) achieved a complete hematological response, which was defined as hematocrit less than 45% without phlebotomy for at least 2 months since last phlebotomy, platelet counts of 400 × 10^9/L or less, leukocytes of 10 × 10^9/L or less, and normal spleen size. The median duration of response was 14.3 months (95% CI, 5.5-30.1).

When evaluated based only on hematocrit, platelets, and leukocytes, 80% (95% CI, 67%-90%) of patients experienced a hematological response with the agent. The median duration of response was 20.8 months (95% CI, 13.0-43.8).

The label includes a box warning for risk of serious disorders related to interferon alfa products stating that these products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. In the pooled safety population of patients treated with ropeginterferon alfa-2b-njft, the most common toxicities included influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain.

Beti-cel Takes Next Step for Transfusion-Requiring β-thalassemia

The FDA has granted priority review to the biologics license application for betibeglogene autotemcel (beti-cel) as treatment for adult, adolescent, and pediatric patients with β-thalassemia across all genotypes who require regular red blood cell transfusions. The agency is expected to decide on the application by May 20, 2022, according to bluebird bio, the developer of the therapy.

Support of the application is based on data from the phase 3 HGB-207 (Northstar-2; NCT02906202) and HGB-212 (Northstar-3; NCT03207009) trials and the phase 1/2 HGB-204 (Northstar; NCT01745120) and HGB-205 (NCT02151526) trials. These 4 serve as the parent trials for patients who may enroll in the 13-year follow-up study, LTF-303 (NCT02633943).

Notably in recent findings from the LTF-303 study, of the 51 patients enrolled, 40 achieved transfusion independence following treatment with beti-cel: 15 of 22 (68%) were treated in the phase 1/2 studies and 25 of 29 (86%) treated in the phase 3 studies.

In data from the Northstar-2 and Northstar-3 trials alone, 32 evaluable patients (89%) met transfusion independence following the gene therapy treatment. Notably, among 22 evaluable pediatric patients, 20 (91%) reached transfusion independence.

Celularity and Imugene Enter Into Potentially “Game-Changing” Collaboration

Chimeric antigen receptor (CAR) T-cell therapies are rapidly shifting the treatment paradigm for a multitude of hematologic malignancies as more products exit development and enter the market. Celularity Inc and Imugene Ltd hope to further add to this growing treatment strategy with their exclusive strategic partnership aimed at exploring the therapeutic potential of CAR T-cell therapy in solid tumors by combining Imugene’s CF33-CD19 oncolytic virus (onCARlytics) and Celularity’s investigational placental-derived CAR T-cell therapy (CyCART-19).

“We found that Imugene’s technology and our technology created a unique opportunity to apply what we know about placental T-cells that can be engineered to express a CAR and their long-term applications in areas such as solid tumors, which up to this point have been unexploited,” said Robert J. Hariri, MD, PhD, founder, chairperson, and chief executive officer of Celularity in Florham Park, New Jersey.

OnCARlytics uses an oncolytic virus, CF33-CD19, to prepare solid tumor cells for treatment with CAR T-cell therapy. After the virus infects a tumor cell, it replicates and induces CD19 expression on the surface of the tumor cell, enabling it to be effectively targeted with CAR T-cell therapy. The lysis of the tumor cell leads to the release of viral particles, which reinitiates the infection of other tumor cells, restarting the process. Imugene exclusively licensed the CF33-CD19 virus from City of Hope in May 2021.

CyCART-19 is an investigational CAR T-cell therapy that is derived from the placenta and cryopreserved. The allogenic, off-the-shelf agent is in development for the treatment of B-cell malignancies and targets CD19.

“Cellularity has what we consider to be the best-in-class CAR T-cells because the cell is derived from the human placenta,” said Andrew Pecora, MD, president of Celularity. “It has the advantage of the greatest amount of natural stemness, meaning that it can proliferate per unit time longer, faster, and better than adult-derived cells. It also has a bit of an ability to evade immune detection. It will be potent and hang around longer.”

The partnership anticipates that combining onCARlytics with CyCART-19 will enable solid tumors to be treated with CAR T-cell therapy, an approach that has previously proven unsuccessful because of a lack of expression of a unique target antigen. If effective, the combination could be used in the treatment of most [patients with] solid tumors, Hariri said.
ONE KEY MAY NOT FIT EVERY LOCK

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Drug Spotlight | ASCIMINIB (SCEMBLIX)

Asciminib Adds to Options for Select Patients With Ph+ CML

by JACKIE COLLINS

BASED ON DATA FROM the phase 3 ASCEMBL trial (NCT03106779) and the phase 1 CABL001X2101 trial (NCT02081378), the FDA has granted accelerated approval to the ABL/BCR-ABL1 tyrosine kinase inhibitor (TKI) asciminib (Scemblix) for the treatment of patients with Philadelphia chromosome (Ph)-positive chronic myeloid leukemia (CML) in chronic phase who have previously been treated with 2 or more TKIs. The FDA also approved asciminib for patients with Ph-positive CML in chronic phase with a T315I mutation.1

Major molecular response (MMR) served as the major efficacy outcome for the decision. In the ASCEMBL trial, patients who received asciminib (n = 157) elicited an MMR rate of 25% (95% CI, 19%-33%) at 24 weeks vs 13% (95% CI, 6.5%-23%) in patients treated with bosutinib (Bosulif; n = 76). In the CABL001X2101 trial, 42% of patients (n = 45; 95% CI, 28%-58%) achieved MMR by 24 weeks and 49% (95% CI, 34%-64%) reached MMR by 96 weeks.2

In an interview with OncologyLive®, Michael J. Mauro, MD, reviewed the results of the 2 trials and considered how this approval will enhance the agent’s potential in these patient populations. Mauro is a hematologist and leader of the Myeloproliferative Neoplasms Program at Memorial Sloan Kettering Cancer Center in New York, New York.

Q Please explain the rationales for the ASCEMBL and CABL001X2101 trials and the importance of identifying the T315I mutation.

The FDA approval of asciminib was based primarily on data from a randomized trial [ASCEMBL], in which investigators looked at patients who did not have the [T315I] mutation but had [been treated with] 2 or more other agents and were lacking response. Patients were eligible to be treated with bosutinib or asciminib, and it was clear from trial [results] that asciminib was [better] able to get patients into MMR and into complete cytogenetic response.

The FDA also had information from the phase 1 trial [CABL001X2101], which was the initial trial of asciminib. Different patient populations were looked at in that study, including a group with the T315I mutation. The results of that subset showed that asciminib was [effective for] patients with that mutation, irrespective of whether they had had prior ponatinib [Incursig].

In the end, we now have a drug that is better than other available options for patients as a third-line treatment. We have a drug that’s safe, tolerable, and effective in a population that previously only had 1 treatment option that was generally expected to be effective—ponatinib. Importantly, the FDA approval said it doesn’t matter when the T315I mutation is identified [for previously treated patients]. If it’s identified [when they receive a] diagnosis—which isn’t very common—or maybe after just 1 treatment, it’s still reasonable to think of asciminib as a treatment [option].

Q What adverse effects should clinicians be aware of when prescribing asciminib?

There is a bit more myelosuppression with asciminib [compared with bosutinib], which may be part of going into remission and response, so that is not necessarily a bad thing...[Also, adverse effects may include] pancreas enzyme elevation and higher blood pressure [with asciminib]. That is something to be monitored and there is a warning in the label of asciminib that cardiovascular disease needs to be assessed, managed, and followed. We need a little bit more time to understand if there is more of a strong concern about that. But at present, it seems quite modest.

For the T315I mutation data [in CABL001X2101], it is important to note that the dose of asciminib is higher in that patient population. It’s 40 mg twice a day or 80 mg once a day for the group of patients without a T315I mutation, and it’s 200 mg twice a day for [patients with] a T315I mutation.

Thankfully, asciminib was well tolerated [at both doses]; a comparative analysis of the 2 [doses] showed no real increase in adverse effects and a similar safety profile.

Q What does the future hold for asciminib?

Asciminib represents a huge advance in CML. We haven’t had a new drug approved in several years. This is a different class of ABL inhibitor; it works by a different mechanism. It’s not just another medication targeting the same region of this abnormal enzyme or kinase. It’s a STAMP—[specifically] targeting the [ABL] myristoyl pocket. It is novel, highly effective, very safe, [and] unique.

Its future might include earlier lines of therapy, [and could be used for treating] patients who haven’t achieved response or safe response or have had tolerability issues even after first treatment. It’s going to be evaluated to help individuals get to treatment cessation if they couldn’t after a first attempt.

It has a bright future and potentially could move up to the front of the pack, perhaps in the frontline or perhaps much earlier in treatment and maybe as a medication to help us put a time frame on CML treatment.

REFERENCES
PIVOTAL CLINICAL TRIALS

ASCEMBL (NCT03106779) was a phase 3 multicenter, randomized, active-controlled, open-label trial evaluating asciminib or bosutinib (Bosulif) in patients with Ph-positive CML in chronic phase previously treated with 2 or more TKIs.

CABL001X2101 (NCT02081378) was a phase 1 multicenter, open-label trial evaluating asciminib in patients with Ph-positive CML in chronic phase with a T315I mutation.

BASELINE PATIENT CHARACTERISTICS IN THE ASCEMBL TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asciminib (n = 157)</th>
<th>Bosutinib (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMR rate</strong></td>
<td></td>
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<tr>
<td>24 weeks (95% CI)</td>
<td>25% (19%-33%)</td>
<td>13% (6.5%-23%)</td>
</tr>
<tr>
<td>48 weeks (95% CI)</td>
<td>29% (22%-37%)</td>
<td>13% (6.5%-23%)</td>
</tr>
<tr>
<td><strong>CCyR rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks (95% CI)</td>
<td>41% (31%-51%)</td>
<td>24% (14%-37%)</td>
</tr>
</tbody>
</table>

BASELINE PATIENT CHARACTERISTICS IN THE CABL001X2101 TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Asciminib (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMR rate</strong></td>
<td></td>
</tr>
<tr>
<td>24 weeks (95% CI)</td>
<td>42% (28%-58%)</td>
</tr>
<tr>
<td>96 weeks (95% CI)</td>
<td>49% (34%-64%)</td>
</tr>
<tr>
<td><strong>Median duration of treatment, weeks (range)</strong></td>
<td>108 (2-215)</td>
</tr>
</tbody>
</table>

Efficacy in the ASCEMBL and CABL001X2101 studies

Commonly reported adverse effects with asciminib

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>All grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>26%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>22%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Headache</td>
<td>19%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

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<tr>
<th>Adverse effect</th>
<th>All grade</th>
<th>Grade 3/4</th>
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</thead>
<tbody>
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</tr>
<tr>
<td>Fatigue</td>
<td>31%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21%</td>
<td>2.1%</td>
</tr>
</tbody>
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Mechanism of action:
- Asciminib is an ABL/BCR-ABL1 TKI that inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein by binding to the ABL1 myristoyl pocket.

Dose:
- For patients with Ph-positive CML in chronic phase previously treated with 2 or more TKIs: 80 mg orally once daily or 40 mg twice daily
- For patients with Ph-positive CML in chronic phase with the T315I mutation: 200 mg orally twice daily

Company: Novartis AG

FDA approval—October 29, 2021
The FDA grants accelerated approval to asciminib (Scemblix) for the treatment of patients with Philadelphia chromosome (Ph)-positive chronic myeloid leukemia (CML) in chronic phase previously treated with 2 or more tyrosine kinase inhibitors (TKIs). The FDA also approved the agent for adult patients with Ph-positive CML in chronic phase with a T315I mutation.

Mechanism of action:
- Asciminib is an ABL/BCR-ABL1 TKI that inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein by binding to the ABL1 myristoyl pocket.

How supplied:
- 20-mg and 40-mg film-coated tablets

References:
PEMBROLIZUMAB (KEYTRUDA) DEMONSTRATED A statistically significant and clinically meaningful improvement in disease-free survival (DFS) vs placebo as a postnephrectomy adjuvant therapy in patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence, and in those who are M1 with no evidence of disease (NED), according to results from the phase 3 KEYNOTE-564 trial (NCT03142334).¹

On November 17, 2021, the FDA approved the PD-1 inhibitor for this patient population following nephrectomy or following nephrectomy and resection of metastatic lesions.²

Results of an interim analysis of KEYNOTE-564 showed that of the 496 patients who received pembrolizumab, 109 patients (22%) had DFS events compared with 151 (30%) patients who received placebo (HR, 0.68; 95% CI, 0.53-0.87; \( P = .001 \)). The median DFS had not yet been reached in either arm. Further, the 24-month DFS rates were 77% (95% CI, 73%-81%) vs 68% (95% CI, 64%-72%), respectively.³

An additional meaningful outcome measure was overall survival (OS). At the time of the interim DFS analysis, OS data were not mature, with 5% deaths in the overall population (N = 994). At a median follow-up of 24.1 months (range, 14.9-41.5), 3.6% of patients in the pembrolizumab arm had experienced an OS event vs 6.6% in the placebo arm (HR, 0.54; 95% CI, 0.30-0.96; \( P = .0164 \)). The 24-month OS rates were 96.5% vs 93.5%, respectively.

KEYNOTE-564 is the first positive phase 3 study of adjuvant immunotherapy in RCC, according to principal investigator Toni K. Choueiri, MD, a 2021 Giants of Cancer Care award winner in the genitourinary cancers category.

“We concluded in KEYNOTE-564 that the first adjuvant immunotherapy to be associated with a benefit is pembrolizumab in terms of DFS,” said Choueiri, director of the Lank Center for Genitourinary Oncology and director of the Kidney Cancer Center at Dana-Farber Cancer Institute in Boston, Massachusetts. “The benefit seemed to be consistent across subgroups despite [them being] small. We believe that pembrolizumab could become a standard of care in the adjuvant setting in RCC.”

Nephrectomy is currently the standard of care treatment for locoregional RCC.⁴ However, there is no globally accepted standard adjuvant therapy supported by high levels of evidence, according to Choueiri. Studies of adjuvant immunotherapy with cytokines have yielded negative results, and adjuvant VEGF-targeted therapy has not shown a consistent benefit.⁵,⁶

In the multicenter, randomized, double-blind, placebo-controlled KEYNOTE-564 trial, investigators assessed if treatment with pembrolizumab following nephrectomy led to significant changes in the 994 patients with clear cell RCC who are at intermediate-high or high risk of recurrence, and those who are M1 with NED.

The median age was 60 years in both the pembrolizumab (range, 27-81) and placebo arms (range, 25-84). At baseline, in the pembrolizumab arm, 427 patients (86.1%) were at intermediate-high risk of recurrence, 40 (8.1%) were at high risk, and 29 (5.8%) were M1 with NED. In the placebo arm, 433 patients (86.9%) were at intermediate-high risk, 36 (7.2%) were at high risk, and 29 (5.8%) were M1 with NED. Additionally, 459 patients (92.5%) had a radical nephrectomy in the investigative arm vs 460 (92.4%) in the control arm; 37 (7.5%) vs 38 patients (7.6%), respectively, had a partial nephrectomy.

Regarding PD-L1, in the pembrolizumab group 124 patients (25%) had a combined positive score (CPS) less than 1 and 365 (73.6%) had 1 or greater; the status was missing for 7 patients (1.4%). In the placebo group, 113 patients (22.7%) had a CPS less than 1, 383 (76.9%) had 1 or greater, and the status for 2 patients (0.4%) was missing.

The median time from randomization to cutoff was 24.1 months (range, 14.9-41.5). Patients were randomized 1:1 to receive 200 mg of pembrolizumab or placebo every 3 weeks until disease recurrence, unacceptable toxicity, or up to 12 months.

After 15 months of minimum follow-up, 260 DFS events occurred—78% of the number planned for the final analysis. Also, 51 OS events occurred—26% of what the number planned for the final analysis.

Investigators have planned additional follow-up to gather mature data from the key secondary end point of OS, according to Choueiri. “Unfortunately, [OS] only had 51 events, making it hard to have any power to connect OS benefits,” he said. “Even with what we saw—at 2 years a 3% difference favoring pembrolizumab, an absolute reduction in death, the hazard ratio of 0.54—we did not meet the stringent criteria for survival benefits. So we continue to follow up on survival.”

Regarding safety, results were in line with expectations and no new safety signals were observed, according to Choueiri. Treatment-related adverse events (TRAEs) occurred in 386 patients (79.1%) in the pembrolizumab arm and 265 patients (53.4%) in the placebo arm; specifically, 92 (18.9%) and 6 patients (1.2%), respectively, experienced grade 3 to 5 TRAEs. None of these TRAEs led to death. Commonly reported TRAEs in the pembrolizumab and placebo groups included fatigue (20.3% vs 14.3%), pruritus (18.6% vs 11.5%), hypothyroidism (17.6% vs 2.6%), diarrhea (15.8% vs 10.3%), and rash (15% vs 7.3%).

REFERENCES
PIVOTAL CLINICAL TRIAL

KEYNOTE-564 (NCT03142334) was a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial evaluating adjuvant pembrolizumab vs placebo following nephrectomy in patients with clear cell RCC who are at intermediate-high risk or high risk of recurrence, and those who are M1 with no evidence of disease.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
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</thead>
<tbody>
<tr>
<td>Pembrolizumab: 60 (27-81) n = 496</td>
</tr>
<tr>
<td>Placebo: 60 (25-84) n = 498</td>
</tr>
</tbody>
</table>

Type of nephrectomy at baseline

- Pembrolizumab: Radical (92.5%) Partial (7.5%)
- Placebo: Radical (92.4%) Partial (7.6%)

Risk of recurrence at baseline

- Pembrolizumab: 81.1% M0 intermediate-high risk 8.1% M0 high risk 5.8% M1 NED
- Placebo: 86.9% M0 intermediate-high risk 7.2% M0 high risk 5.8% M1 NED

Number of cycles of prior chemotherapy (%)

- Pembrolizumab: CPS < 1 1.4% CPS ≥ 1 25.0%
- Placebo: CPS < 1 0.4% CPS ≥ 1 76.9%

REFERENCES


WARNINGS AND PRECAUTIONS

- Severe and fatal immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeneic hematopoietic stem cell transplantation
- Embryo-fetal toxicity

COMMONLY REPORTED ADVERSE EVENTS IN THE KEYNOTE-564 STUDY

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pembrolizumab (n = 488)</th>
<th>Placebo (n = 496)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>41%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Rash</td>
<td>30%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>21%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cough</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>14%</td>
<td>3.7%</td>
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<tr>
<td>Acute kidney injury</td>
<td>13%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12%</td>
<td>0.2%</td>
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<tr>
<td>Abdominal pain</td>
<td>11%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Efficacy Findings in the KEYNOTE-564 Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab (n = 496)</th>
<th>Placebo (n = 498)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event</td>
<td>109 (22%)</td>
<td>151 (30%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>24-month DFS rate (95% CI)</td>
<td>77% (73%-81%)</td>
<td>68% (64%-72%)</td>
</tr>
</tbody>
</table>

FDA Approval—November 17, 2021

The FDA has approved pembrolizumab (Keytruda) for the adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Mechanism of action:

- Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

How supplied:

- 100 mg/4 mL (25 mg/mL) solution in a single-dose vial
- Dose: 200 mg every 3 weeks or 400 mg
- Company: Merck

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- Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

How supplied:

- 100 mg/4 mL (25 mg/mL) solution in a single-dose vial
- Dose: 200 mg every 3 weeks or 400 mg
- Company: Merck
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

**Infections:** Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis 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.

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

**Cardiac Arrhythmias and Cardiac Failure:** Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

**Hypertension:** Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

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

ADVERSE REACTIONS

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

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

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

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

DRUG INTERACTIONS

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

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

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

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib)

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-30 times higher than those reported in patients with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. [See Use in Specific Populations].

ADVERSE REACTIONS

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

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

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to IMBRUVICA in 6 trials as a single agent at 420 mg orally once daily in 475 patients and at 560 mg orally once daily in 174 patients and in 4 trials administered in combination with other drugs at 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies, 87% were exposed for 6 months or longer and 68% were exposed for greater than one year. In this pooled safety population, 1,476 patients with B-cell malignancies, the most common adverse reactions (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure to IMBRUVICA in one single-arm, open-label clinical trial (Study 1102) and five randomized controlled clinical trials (RESONATE, RESONATE-2, HELIOS, ILLUMINATE, and E1912) in patients with CLL/SLL (n=2,016 total, including n=1,133 patients exposed to IMBRUVICA). In general, patients with creatinine clearance (CrCl) ≥ 30 mL/min, ALT ≥ 2.5 x ULN, or total bilirubin ≥ 1.5 x ULN (unless of non-hepatic origin) were excluded from these trials. In Study E1912, patients with AST or ALT > 3 x ULN or total bilirubin > 2.5 x ULN were excluded. Study 1102 included 51 patients with previously treated CLL/SLL. RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab. RESONATE-2 included 267 randomized patients with treatment naive CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil. HELIOS enrolled 374 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with BR or placebo in combination with BR. ILLUMINATE included 228 randomized patients with treatment naive CLL/SLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab. E1912 included 510 patients with previously untreated CLL/SLL who were 70 years or younger and received IMBRUVICA in combination with rituximab or received fludarabine, cyclophosphamide, and rituximab (FCR).

The most common adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥ 30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising, and nausea.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, neutropenia, arthralgia, rash, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in approximately 5% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from Study 1102 (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 1 and 2.
Table 1: 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>Dysepsis</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>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>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 spasm</td>
<td>18</td>
<td>2</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>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>Vascular disorders</td>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td></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>
</tbody>
</table>

1 One patient death due to histiocytic sarcoma.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

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

* Based on laboratory measurements per IWCLL criteria and adverse reactions. Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

RESONATE: Adverse reactions and laboratory abnormalities described below in Tables 3 and 4 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

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

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

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

* Includes multiple ADR terms

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>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.

RESONATE-2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 11.1 months in RESONATE-2.
Table 5: Adverse Reactions Reported in ≥10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
<td>30</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Bruising*</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term. The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm. *
* Includes multiple ADR terms

Table 6: 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></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</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.
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Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in ILLUMINATE (continued)

<table>
<thead>
<tr>
<th>Body System/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>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34 3 0 0</td>
<td>10 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 0 0 1</td>
<td>12 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 0 0 0</td>
<td>3 0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>33 1 23 3</td>
<td>0 0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22 1 10 0</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 0 6 0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27 1 12 0</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25 2 58 8</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>25 1 9 0</td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>17 4 4 3</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 2 26 1</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 0 17 2</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12 0 7 0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16 9 9 4†</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 1 6 0</td>
<td></td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13 1 3 0</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 3 7 1</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 0 3 0</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11 0 2 0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13 1 0 0</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 5 0 0</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 0 4 0</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>80 2 78 3</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28 1 17 0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27 1 27 1</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>23 2 8 0</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* Includes multiple ADR terms

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

<table>
<thead>
<tr>
<th></th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Hematology abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53 30 70 44</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43 7 69 25</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26 0 51 2</td>
<td></td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38 1 17 1</td>
<td></td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>30 2 15 0</td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>25 3 23 &lt;1</td>
<td></td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria.
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Additional Important Adverse Reactions: Cardiac Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 18.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 0.4% versus 1.8% and for Grade 3 or greater was 0.4% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) of any grade was 1% versus 0.4% and for Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea: In randomized controlled trials (n=2,115; median treatment duration of 18.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,605 of these patients, the median time to first onset was 19 days (range, 0 to 778) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 471) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 58) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance: In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and 1% Grade 2 and 3).

Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 477) versus 105 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analyzed. The median treatment duration was 51 months (range, 0 to 98 months) for CLL/SLL, 11 months (range, 0 to 97 months) for MCL, and 47 months (range, 0 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the over-all prevalence of hypertension was 12%.

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

• Hepatobiliary disorders: hepatotoxicity including acute and/or fulminant hepatitis, hepatic cirrhosis
• Hematopoietic disorders: interstitial lung disease
• Metabolic and nutrition disorders: tumor lysis syndrome
• Immune system disorders: anaphylactic shock, angioedema, urticaria
• Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), erythema multiforme, toxic epidermal necrolysis
• Infections: hepatitis B reactivation
• Nervous system disorders: peripheral neuropathy

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DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with concomitant strong or moderate CYP3A inhibitors 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 concomitant psoriasis, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. If these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate 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 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 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 60 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MZL) and 25 times the exposure in patients with CLL/SLL or Waldenström’s Macroglobulinemia (WM) administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily. Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and 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 2.8 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

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

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

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

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

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

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.
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Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Active ingredient made in China.

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

Patent http://www.imbruvica.com
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TOP TWEETS

ADCs, Checkpoint Inhibitors Generate Discussion at ESMO 2021 in Lung Cancer
@AlexSpiraMDPhD @VCSpecialists @myESMO #icsm
bit.ly/2ZqdPR7

Though the available COVID-19 vaccines have shown high efficacy in the general population, their long-term safety and efficacy among patients with cancer had been underrepresented. #COVID19 #oncology
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Two indications have been granted by the FDA to the Nectin-4-directed antibody, enfortumab vedotin-ejfv, marking a shift in the treatment landscape for patients with advanced urothelial carcinoma. @tompowles1 @CR_UK #blcsm
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As the autumn and winter conference season approaches, Curtis Lachowiez, MD, reflects on the impact 2020 left on the field of oncology. @CLachowiez @MDAndersonNews #Oncology
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ONCLIVE ONAIR® PODCAST SPOTLIGHT

FDA APPROVAL INSIGHTS AMIVANTAMAB AND MOBOCERTINIB IN EGFR EXON 20 INSERTION + NSCLC
Sandip P. Patel, MD, discusses the FDA approvals of amivantamab-vmjw (Rybrevant) and mobocertinib (Exkivity) for patients with non–small cell lung cancer (NSCLC) who harbor EGFR exon 20 insertion mutations, and future research directions in this subset of lung cancer.
LISTEN: bit.ly/3iVfcO3

ONCLIVE ON AIR® MOORE VOICES EXCITEMENT OVER VS-6766 PLUS DEFACTINIB IN OVARIAN CANCER
Kathleen Moore, MD, discusses the basis for studying the combination of VS-6766 and deactinib in recurrent low-grade serous ovarian cancer, data from the phase 1/2 FRAME trial (NCT03875820), and the potential role for the combination in clinical practice.
LISTEN: bit.ly/3iZ1iKU

ONCLIVE ON AIR® ABID ON OPTIMIZING COVID-19 VACCINES IN CAR T-CELL THERAPY RECIPIENTS
Muhammad Bilal Abid, MD, MRCP, discusses his recent review paper that outlines immuno-compromising factors for chimeric antigen receptor (CAR) T-cell therapy recipients, the immunogenic potential of different COVID-19 vaccines, and determinants of vaccine responses.
LISTEN: bit.ly/2ZkVm8J

SPOTLIGHT

TRASTUZUMAB DERUXTECAN REPRESENTS POTENTIAL NEW SECOND-LINE STANDARD IN HER2+ METASTATIC GASTRIC/GEJ CANCER
Updated data from the phase 2 DESTINY-Gastric02 trial (NCT04014075) showed that fam-trastuzumab deruxtecan-nkx (Enhertu) elicited promising response rates as a second-line therapy in Western patients with HER2-positive gastric/gastroesophageal junction (GEJ) cancer, further underscoring the need for molecular profiling to determine who are the best candidates to receive the antibody-drug conjugate (ADC), according to John L. Marshall, MD.

In an interview with OncLive®, Marshall discussed the results of the trial, the importance of molecular profiling, and future considerations for the ADC.

“This is a breakthrough in [that we saw a] very high response rate in [patients who received trastuzumab deruxtecan in later] lines [of therapy],” Marshall said. “This is what we wanted to see: it is a potent HER2-targeted treatment. [These findings] further emphasize the need for all of us to have good molecular profiling on our patients with gastric cancer, so we know whether they are HER2 positive [and can receive this treatment].”
READ MORE: bit.ly/3Ec7RSE
**THE PROMISE OF LIQUID BIOPSIES FOR CANCER DIAGNOSIS**

by Liz Kwo, MD, MBA, MPH; and Jenna Aronson

In recent years, the clinical development of liquid biopsies for cancer, a revolutionary screening tool, has created great optimism. They have been used for diagnosing and screening non–small cell lung cancer or as a companion diagnostic for other types of cancers, such as gastrointestinal, colorectal, breast, prostate, and ovarian cancer. Currently, liquid biopsies are most commonly used as a complementary technique to standard tissue biopsies. Standard tissue biopsies are still the mainstay for cancer diagnosis, but for those patients who are unable to undergo or whose tumors are not amenable to invasive biopsies, liquid biopsies hold promise.

READ MORE: bit.ly/2ZqXgVb

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**RAPID READOUTS**

**IKEMA SUBGROUP ANALYSIS IN RELAPSED MULTIPLE MYELOMA**

Investigators reported that the addition of isatuximab-irfc (Sarcilis) to carfilzomib (Kyprolis) plus dexamethasone showed an improved progression-free survival in patients with relapsed multiple myeloma and high-risk cytogenetic abnormalities, along with an improved disease response in patients with isolated or combined gain(1q21) with high-risk cytogenetic abnormalities. Timothy M. Schmidt, MD, discusses data from the subgroup analysis of the phase 3 IKEMA trial (NCT03275285), presented at the 2021 American Society of Clinical Annual Meeting. Isatuximab/carfilzomib/dexamethasone is now a potential new treatment option for this difficult-to-treat subgroup.

WATCH: bit.ly/3jvLAH

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**ODENZA TRIAL**

Tian Zhang, MD, unpacks the cognitive assessment data of the phase 2 ODENZA trial (NCT03314324), presented at the European Society for Medical Oncology Congress 2021. The data demonstrated that darolutamide (Nubeqa) was associated with a statistically significant benefit in verbal learning and verbal memory compared with enzalutamide (Xtandi) in patients with early metastatic castration-resistant prostate cancer.

WATCH: bit.ly/3jA7pWu

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**RADIOEMBOLIZATION WITH CHEMOTHERAPY FOR COLORECTAL LIVER METASTASES**

Riad Salem, MD, MBA, highlights key data from the phase 3 EPOCH trial (NCT01483027), which evaluated yttrium-90 transarterial radioembolization (Y-90 TARE) with chemotherapy in the second-line treatment of patients with colorectal liver metastases. The study elicited statistically significant efficacy data and study success criteria were met.

WATCH: bit.ly/3vHFtX9

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**PHASE 1 COHORT OF TRANSCEND-CLL-004 STUDY**

William G. Wierda, MD, offers his analysis of data from the phase 1 cohort of the TRANSCEND-CLL-004 trial (NCT03331198), which showed that treatment with lisocabtagene-mara-leucel (Breyanzi) and ibrutinib (Imbruvica) produced high overall response rates in patients with relapsed or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma.

WATCH: bit.ly/3jyjhE4

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**NOTABLE QUOTABLES**

“Almost all the discussions and the points that we debate now are very far from the sorts of things we would have been debating [15 years ago], and in many respects is indicative of substantial success. Although lung cancer remains a difficult disease, it is one for which people should be hopeful.”

—Edward B. Garon, MD
University of California, Los Angeles

READ MORE: bit.ly/3Eh7w0S

“Patients with early-stage HER2-positive breast cancer have an excellent prognosis. They used to have the worst prognosis, but because of [several approved] therapies... these patients have [a better] prognosis.”

—Francisco Javier Esteva, MD, PhD
Northwell Health Cancer Institute

READ MORE: bit.ly/3vGIdm1

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**JOURNAL SPOTLIGHT**

For breaking news, interviews with key opinion leaders, conference coverage, and more, follow us on Twitter, @OncLive, or use your smartphone to scan this QR code.
**IMFINZI + EP: The only 10 combination with 3-year overall survival in 1L ES-SCLC**

**NCCN CATEGORY 1, PREFERRED**

Durvalumab (IMFINZI®) + etoposide with either cisplatin or carboplatin is a Category 1, preferred treatment option for first-line ES-SCLC.

See the new 3-year analysis at IMFINZIhcp.com/sclc

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

**Select Safety Information**
There are no contraindications for IMFINZI® (durvalumab).

**Immune-Mediated Adverse Reactions**
Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions.

Please see Brief Summary of complete Prescribing Information on adjacent pages.
IMFINZI + EP: Sustained overall survival benefit at 3 years

OVERALL SURVIVAL AT 3-YEAR PLANNED EXPLORATORY ANALYSIS

(median duration of follow-up 39.4 months)

HR=0.71
(95% CI, 0.60-0.86)

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>IMFINZI + EP (n=268)</th>
<th>EP (n=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>268</td>
<td>269</td>
</tr>
<tr>
<td>24 months</td>
<td>243</td>
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<td>36 months</td>
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</tbody>
</table>

12 months
52.8%
39.3%
24 months
22.9%
13.9%
36 months
17.6%
5.8%

SUPERIOR OVERALL SURVIVAL AT INTERIM ANALYSIS

13-MONTH mOS
WITH IMFINZI + EP
HR=0.73
(95% CI, 0.59-0.91; P=0.0047)

10.3-MONTH mOS
WITH EP ALONE

Safety and tolerability

- Serious adverse reactions occurred in 31% of patients receiving IMFINZI + EP at the interim analysis and in 33% of patients receiving IMFINZI + EP at the 3-year analysis.
- The most frequent serious adverse reactions reported in ≥1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%), and chronic obstructive pulmonary disease (1.1%).
- The most common adverse reactions (occurring in ≥20% of patients) were nausea, fatigue/asthenia, and alopecia.
- Discontinuation rates were the same with IMFINZI + EP and EP alone (9% in both arms).
- Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI + EP. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients).

HR=hazard ratio; CI=confidence interval; mOS=median overall survival; OS=overall survival; D3W=once every 3 weeks; D4W=once every 4 weeks.

1The planned exploratory 3-year OS analysis was conducted at ~3 years after the last patient was randomized, and was not formally tested for statistical significance. At the time of the 3-year analysis, mOS was 12.9 months (95% CI, 11.3-14.7) with IMFINZI + EP vs 10.5 months (95% CI, 9.3-11.2) with EP alone (HR=0.71; 95% CI, 0.59-0.91; P=0.0047).

2The planned interim analysis of the IMFINZI + EP and EP alone arms are the estimated proportion of patients alive based on the 3-year analysis.

3The CASPIAN study is an open-label, multicenter, Phase III study of 805 treatment-naive patients with ES-SCLC who were randomized 1:1:1 between 3 arms. Patients received IMFINZI 1500 mg plus either carboplatin or cisplatin and etoposide D3W (n=269) for 4-6 cycles. The third arm was IMFINZI plus an Investigational Agent and EP followed by IMFINZI maintenance (n=268). FDA approval was based on the results from the planned interim analysis of the IMFINZI + EP and EP alone arms. Overall survival was the primary endpoint. At the time of the planned interim overall survival analysis with a median duration of follow-up of 14.2 months, mOS was 13 months (95% CI, 11.5-14.8) with IMFINZI + EP vs 10.3 months (95% CI, 9.3-11.2) with EP alone (HR=0.73; 95% CI, 0.59-0.91; P=0.0047).
Select Safety Information (continued)

Immune-Mediated Adverse Reactions (continued)

Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue IMFINZI depending on severity. See Dosing and Administration for specific details. In general, if IMFINZI requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients who did not receive recent prior radiation, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. In patients who received recent prior radiation, the incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation within 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (87/475) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475), 1.1% were fatal and 2.7% were Grade 3 adverse reactions. The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar in patients who received IMFINZI as a single agent or with ES-SCLC when in combination with chemotherapy.

Immune-Mediated Colitis

IMFINZI can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 3 (0.4%) adverse reactions.

Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions.

Immune-Mediated Endocrinopathies

- **Adrenal Insufficiency**: IMFINZI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

- **Hypophysitis**: IMFINZI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated. Grade 3 hypophysitis/hypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI.

- **Thyroid Disorders**: IMFINZI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.

- **Thyroiditis**: Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

- **Hyperthyroidism**: Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI.

- **Hypothyroidism**: Immune-mediated hypothyroidism occurred in 8.3% (158/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

- **Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis**: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Grade 3 immune-mediated type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI.

Immune-Mediated Nephritis with Renal Dysfunction

IMFINZI can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

Immune-Mediated Dermatological Reactions

IMFINZI can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), have occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Immune-mediated rash or dermatitis occurred in 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.4%) adverse reactions.

Other Immune-Mediated Adverse Reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMFINZI or were reported with the use of other PD-1/PD-L1 blocking antibodies.

- **Cardiac/vascular**: Myocarditis, pericarditis, vasculitis.

- **Nervous system**: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis.
Immune-Mediated Endocrinopathies

Grade 3 (1.4%) adverse reactions. In patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 5 (0.0%) adverse reactions. Adrenal insufficiency occurred in 0.5% (11/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

Infusion-Related Reactions

IMFINZI can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue IMFINZI based on the severity. See Dosing and Administration for specific details. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses. Infusion-related reactions occurred in 2.2% (42/1889) of patients receiving IMFINZI, including Grade 3 (0.3%) adverse reactions.

Complications of Allogeneic HSCT after IMFINZI

Fetal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/L1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI.

Lactation

There is no information regarding the presence of IMFINZI in breastmilk; however, because of the potential for adverse reactions in breastfed infants from IMFINZI, advise women not to breastfeed during treatment and for at least 3 months after the last dose.

Adverse Reactions

- **In patients with extensive-stage SCLC in the CASPIAN study receiving IMFINZI plus chemotherapy (n=265), the most common adverse reactions (≥20%) were nausea (34%), fatigue/asthenia (32%), and anemia (31%). The most common Grade 3 or 4 adverse reaction (≥3%) was treatment-related death (1.9%).**

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

Please see Brief Summary of complete Prescribing Information on adjacent pages.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

References:

IMFINZI® (durvalumab) injection, for intravenous use
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
Small Cell Lung Cancer
IMFINZI, in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

DOSAGE AND ADMINISTRATION
Recommended Dosage
The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with chemotherapy are presented in Table 1. [see Clinical Studies (14) in the full Prescribing Information]. IMFINZI is administered as an intravenous infusion over 60 minutes.

Table 1. Recommended Dosages of IMFINZI

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended IMFINZI dosage</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES-SCLC</td>
<td>Patients with a body weight of 30 kg and more: 1500 mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as a single agent</td>
<td>Until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>Patients with a body weight of less than 30 kg: 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 10 mg/kg every 2 weeks as a single agent</td>
<td></td>
</tr>
</tbody>
</table>

Administer IMFINZI prior to chemotherapy on the same day. When IMFINZI is administered in combination with etoposide and carboplatin or cisplatin for dose-limiting toxicity, IMFINZI should be administered following completion of chemotherapy. If IMFINZI is to be administered with etoposide, chemotherapy should be given at least 30 minutes before or after IMFINZI

Dosage Modifications for Adverse Reactions
No dose reduction for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of equivalent prednisone per day within 12 weeks of initiating corticosteroids.

Dosage modifications for IMFINZI for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2. Recommended Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1) in the full Prescribing Information]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Grade 1</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Colitis</td>
<td>Grade 1</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>Grade 2 or 3</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis with no tumor involvement of the liver</td>
<td>AST or ALT increases to more than 3 times ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>AST or ALT increases to more than 8 times ULN or total bilirubin increases to more than 3 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis with tumor involvement of the liver</td>
<td>AST or ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN or AST or ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>AST or ALT increases to more than 10 times ULN or total bilirubin increases to more than 3 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Grade 3 or 4</td>
<td>Withhold</td>
</tr>
<tr>
<td>Nephritis with Renal Dysfunction</td>
<td>Grade 2 or 3 increased blood creatinine</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 4 increased blood creatinine</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Exfoliative Dermatologic Conditions</td>
<td>Obscured SJS, TEN, or DRESS</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Grade 2, 3, or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Neurological Toxicities</td>
<td>Grade 2</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions [see Warnings and Precautions (5.2) in the full Prescribing Information]</td>
<td>Grade 1 or 2</td>
<td>Interrupt or slow the rate of infusion</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

Preparation and Administration
Preparation
- Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or if visible particles are observed.
- Do not shake the vial.
- Withhold the required volume from the vial(s) of IMFINZI and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 0.9% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL.
- Discard partially used or empty vials of IMFINZI.

Storage of Infusion Solution
IMFINZI does not contain a preservative.

Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the time from preparation should not exceed:
- 28 days in a refrigerator at 2°C to 8°C (36°F to 46°F)
- 8 hours at room temperature up to 25°C (77°F)
- Do not freeze.
- Do not shake.

Administration
- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other drugs through the same infusion line.

CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

Immune-Mediated Adverse Reactions
IMFINZI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing the inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2) in the full Prescribing Information]. In general, if IMFINZI requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., dermatopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis
IMFINZI can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

In Patients Who Did Not Receive Prior Thoracic Radiation
In patients who received IMFINZI on clinical trials in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 5 patients. Systemic corticosteroids were required in 19 patients (18/34) with pneumonitis who did not receive chemoradiation prior to initiation of IMFINZI.

In Patients Who Received Prior Thoracic Radiation
The incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation for 42 days prior to initiation of IMFINZI in PACE-HC was 18.3% (57/310) in patients receiving IMFINZI and 12.8% (302/234) in patients receiving placebo. Of the patients who received IMFINZI (475) 11.1% were fatal and 2.7% were Grade 3 adverse reactions. Events resolved in 50 of the 87 patients and resulted in permanent discontinuation in 27 patients. Systemic corticosteroids were required in 64 patients (64/87) with pneumonitis who had received chemoradiation prior to initiation of IMFINZI while 2 patients required use of infliximab with high-dose steroids. The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar whether IMFINZI was given as a single agent in patients with various cancers in a pooled data set or in patients with ES-SCLC when given in combination with chemotherapy.

Immune-Mediated Colitis
IMFINZI can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with colitis/refractory-immune-mediated colitis. In cases of colitis/refractory-colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 3 (0.4%) adverse reactions. Events resolved in 27 of the 37 patients and resulted in permanent discontinuation in 8 patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 2 patients (2/37) required other immunosuppressants (e.g. infliximab, mycophenolate).
Immune-Mediated Adverse Reactions

Immune-Mediated Hepatitis

IMFINZI® (durvalumab) injection, for intravenous use 2

Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.1%), and Grade 3 (1.4%) adverse reactions. Events resolved in 21 of the 52 patients and resulted in permanent discontinuation of IMFINZI in 6 patients. Systemic corticosteroids were required in all patients with immune-mediated hepatitis, while 2 patients (0.5%) required use of mycophenolate with high-dose steroids.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

IMFINZI® can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.2) in the full Prescribing Information]. Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (0.1%) adverse reactions. Events resolved in 1 of the 9 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.

Gastrointestinal:

Duodenitis.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L-1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/L-1 blocking antibody prior to or after an allogeneic HSCT.

Immune-Mediated Adverse Reactions

The following adverse reactions are discussed in greater detail in other sections of the labeling.

• Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1) in the full Prescribing Information]

• Infusion-Realted Reactions [see Warnings and Precautions (5.2) in the full Prescribing Information]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflect exposure to IMFINZI in 1869 patients from the PACIFIC study (a randomized, placebo-controlled study that enrolled 475 patients with Stage III NSCLC). Study 1108 [an open-label, single-arm, multicohort study that enrolled 970 patients with advanced solid tumors], and an additional open-label, single-arm trial that enrolled 444 patients with metastatic lung cancer, an indication for which durvalumab is not approved. In these trials, IMFINZI was administered at a dose of 10 mg/kg every 2 weeks. Among the 1869 patients, 35% were exposed for 6 months or more and 16% were exposed for 12 months or more. The data also reflect exposure to IMFINZI in combination with chemotherapy in 266 patients from the CASPIAN study (a randomized, open-label study in patients with ES-SCLC). In the CASPIAN study, IMFINZI was administered at a dose of 1500 mg every 3 or 4 weeks.

The data described in this section reflect exposure to IMFINZI in patients with ES-SCLC enrolled in the CASPIAN study.

Table 5. Adverse Reactions Occurring in > 10% Patients in the CASPIAN study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMFINZI with etoposide and either carboplatin or cisplatin</td>
<td>N = 295</td>
<td></td>
<td>N = 286</td>
<td></td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Cough/Productive Cough</td>
<td>15</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal/Genitourinary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>0.4</td>
<td>14</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>0</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>1.1</td>
<td>11</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Disruption of PD-L1 signaling was shown to result in an increase in fetal loss. Therefore, it is essential to maintain maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, there was no significant increase in prematurity or stillbirth in normal, immune-competent controls. The risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders has been reported in PD-1 knockout mice.

Lactation

Risk Summary

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (see Data).

Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data

In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels (approximately) 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature neonatal death.

Females and Males of Reproductive Potential

Contraception

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

Embryo-Fetal Toxicity

Embryo-Fetal Toxicity

Advise females of reproductive potential to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.

Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.

Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain.

Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypopituitarism.

Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Dermatological Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermatological reactions.

Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis.

Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.

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Immunotherapy Paves Path for New Standards of Care in Gastroesophageal Cancers

by KANAK PARMAR, MD; and SARBAJIT MUKHERJEE, MD, MS

GASTROESOPHAGEAL CANCERS (GEC), which consist of esophageal, gastroesophageal junction (GEJ), and gastric cancers, are the most prevalent gastrointestinal cancers worldwide. Globally, more than 600,000 new esophageal cancer cases are detected annually, claiming 544,000 lives. On the other hand, more than 1 million new gastric cancer cases are detected annually worldwide, leading to an estimated 769,000 deaths.

In 2021, several new FDA approvals involving the use of immune checkpoint inhibitors changed the treatment landscape in GEC. Nivolumab (Opdivo) was approved as the first adjuvant treatment in patients with completely resected esophageal/GEJ cancer following chemoradiation therapy (CRT) who had residual pathologic disease. Furthermore, pembrolizumab (Keytruda) and nivolumab were also approved for the frontline treatment of patients with metastatic GEC. These immune checkpoint inhibitors have a manageable toxicity profile while significantly improving clinical outcomes in patients.

However, not all patients benefit similarly from using this class of agents. PD-L1 expression has been commonly used as a biomarker, and patients with higher PD-L1 expression seem to benefit more from checkpoint inhibitors. Therefore, it is crucial to understand and interpret the results from the landmark clinical trials in the context of recent FDA approvals.

DEFINING THE ROLE OF IMMUNOTHERAPY AS ADJUVANT TREATMENT OF GASTROESOPHAGEAL CANCERS

Neoadjuvant CRT followed by surgery is a widely used treatment strategy for patients with resectable esophageal or GEJ cancer. Studies in murine models show that radiotherapy and chemotherapy can exert immunomodulatory effects, resulting in synergistic treatment responses when combined with immunotherapy. CheckMate 577 (NCT02743494) was a global, randomized, double-blind, placebo-controlled phase 3 trial that evaluated nivolumab vs placebo as an adjuvant treatment after neoadjuvant CRT and surgery for patients with esophageal or GEJ cancer with residual pathological disease. Results showed that nivolumab was associated with a significant improvement in disease-free survival at 22.4 months (95% CI, 16.6-34.0) compared with 11.0 months (95% CI, 8.3-14.3) with placebo, leading to a 31% reduction in the risk of recurrence or death (HR, 0.69; 96.4% CI, 0.56-0.86; P < .001). Overall survival (OS) data favored nivolumab over placebo across most prespecified subgroups and regardless of PD-L1 status. Regarding safety, serious adverse events (AE) related to nivolumab that led to discontinuation of the trial regimen were reported in less than 10% of patients.

The data served as the basis for the May 2021 FDA approval of nivolumab for the adjuvant treatment of completely resected esophageal or GEJ cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy. Currently, the global, randomized, phase 3 KEYNOTE-585 trial (NCT03221426) is investigating the role of both neoadjuvant and adjuvant pembrolizumab and chemotherapy in patients with localized gastric or GEJ adenocarcinoma.

Given the positive results of CheckMate 577, an important question in the field is whether the adjuvant use of checkpoint inhibitor therapy may improve outcomes in patients undergoing definitive CRT without surgery. This is being investigated in the ongoing KEYNOTE-975 study (NCT04210115). Use of immune checkpoint inhibitors in the neoadjuvant setting is also being investigated.

IMMUNOTHERAPY AS A NEW FIRST-LINE THERAPY: LESSONS LEARNED FROM KEYNOTE-590, CHECKMATE 649, CHECKMATE 648, AND KEYNOTE-811

A combination of fluoropyrimidine plus platinum-based chemotherapy is used as the standard first-line treatment for patients with advanced or metastatic GEC. Several studies, including KEYNOTE-059 (NCT02335411), KEYNOTE-181 (NCT02564263), CheckMate 032 (NCT01928394), ATTRACTION-2 (NCT02267343), and ATTRACTION-3 (NCT02569242), demonstrated the activity of immune checkpoint inhibitors in refractory GEC. However, results of a chemoimmunotherapy approach in the frontline setting have not been inspiring until just recently.

KEYNOTE-590

The global, phase 3 KEYNOTE-590 trial (NCT03189719) compared pembrolizumab and chemotherapy against...
placebo plus chemotherapy in patients with unresectable, locally advanced, or metastatic esophageal cancer or GEJ adenocarcinoma in the first-line setting. OS was significantly improved with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in all randomized patients at 12.4 months vs 9.8 months (HR, 0.73; 95% CI, 0.62-0.86; \( P < .0001 \)). Specifically in esophageal squamous cell carcinoma (ESCC), the median OS was 12.6 months and 9.8 months, respectively (HR, 0.72; 95% CI, 0.60-0.88; \( P = .0006 \)), leading to the March 2021 FDA approval of pembrolizumab in this setting. However, further analysis showed that the benefit was less prominent in esophageal adenocarcinoma (EAC; HR, 0.74; 95% CI, 0.54-1.02) and in patients with a PD-L1 CPS of less than 10 (HR, 0.86; 95% CI, 0.68-1.10). In patients with a PD-L1 combined positive score (CPS) of 10 or higher, the median OS was 13.5 months vs 9.4 months (HR, 0.62; 95% CI, 0.49-0.78; \( P < .0001 \)). Specifically in esophageal squamous cell carcinoma (ESCC), the median OS was 12.6 months and 9.8 months, respectively (HR, 0.72; 95% CI, 0.60-0.88; \( P = .0006 \)), leading to the March 2021 FDA approval of pembrolizumab in this setting. However, further analysis showed that the benefit was less prominent in esophageal adenocarcinoma (EAC; HR, 0.74; 95% CI, 0.54-1.02) and in patients with a PD-L1 CPS of less than 10 (HR, 0.86; 95% CI, 0.68-1.10).

**CheckMate 469**

CheckMate 469 (NCT02872116) was a global, open-label, phase 3 trial that randomized previously untreated patients with unresectable, advanced, or metastatic gastric/GEJ/EAC with no known HER2 positivity to nivolumab and ipilimumab (Yervoy), nivolumab and chemotherapy, or chemotherapy alone. Nivolumab and chemotherapy improved OS in patients with a PD-L1 CPS of 5 or higher at 14.4 months (95% CI, 13.1-16.2) vs 11.1 months (95% CI, 10.1-12.1) with chemotherapy alone (HR, 0.71; 98.4% CI, 0.59-0.86; \( P < .0001 \)). In all randomized patients, the median OS was 13.8 months vs 11.6 months, respectively (HR, 0.77; 99.3% CI, 0.68-0.94; \( P < .0001 \)) but the combination of nivolumab and ipilimumab did not significantly improve survival compared with chemotherapy.

Based on the results of this study, nivolumab was approved by the FDA in April 2021 for use in this patient population, regardless of PD-L1 status. Interestingly, in a subgroup analysis, patients with a CPS of less than 5 did not seem to benefit from the addition of nivolumab (HR, 0.94; 95% CI, 0.78-1.13). These results seem to suggest that, at least for metastatic/unresectable HER2-negative GEC, patients with a higher CPS are likely to benefit more from the addition of immune checkpoint inhibitors.

**CheckMate 648**

CheckMate 648 (NCT03143153) was the first global, phase 3 study to evaluate a combination immunotherapy regimen consisting of nivolumab and ipilimumab and nivolumab and chemotherapy against standard chemotherapy as first-line treatment in patients with unresectable advanced, recurrent, or metastatic ESCC. In all randomized patients, the combination immunotherapy regimen improved OS over chemotherapy at 12.8 months (95% CI, 11.3-15.5) vs 10.7 months (95% CI, 9.4-11.9), respectively (\( P = .011 \)). This study also found improved outcomes in terms of OS when combining nivolumab with chemotherapy compared with chemotherapy alone at 13.2 months (95% CI, 11.1-15.7) vs 10.7 months (95% CI, 9.4-11.9), respectively (\( P = .0021 \)) in all randomized patients. No new safety signals were observed. This study presented nivolumab and chemotherapy as a new potential treatment option in the frontline treatment of metastatic ESCC, and the results also suggest that some patients with ESCC may benefit from a chemotherapy-free approach (Table 13-15). Since the ToGA trial (NCT01041404), trastuzumab (Herceptin) plus chemotherapy has been the standard first-line treatment for patients with metastatic or unresectable HER2-positive gastric or GEJ adenocarcinoma. Because some recent phase 2 studies showed great antitumor activity and a manageable safety profile of pembrolizumab combined with trastuzumab and chemotherapy, KEYNOTE-811 (NCT03615326) was conducted to assess the efficacy of this regimen. This was a randomized, double-blind, placebo-controlled trial in patients with metastatic HER2-positive gastric or GEJ adenocarcinoma who did not receive prior systemic treatment for their metastatic disease. Patients were randomized to receive pembrolizumab or placebo in combination with trastuzumab and chemotherapy. Patients in the pembrolizumab arm had an objective response rate of 74.4% (95% CI, 66.2%-81.6%) compared with 51.9% (95% CI, 43.0%-60.7%) in those in the placebo arm. The duration of response was also improved in the pembrolizumab arm, and the AEIs

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**Table.** Overall Survival Benefits With Frontline Immunotherapy GEC Cancers\(^{13-15}\)

<table>
<thead>
<tr>
<th>Trial (ClinicalTrials.gov identifier)</th>
<th>Disease state, all frontline setting</th>
<th>Intervention</th>
<th>Median OS in all randomized patients</th>
<th>HR</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-590 (NCT03189719)</td>
<td>Unresectable, locally advanced, or metastatic esophageal cancer or GEJ adenocarcinoma</td>
<td>Pembrolizumab/chemotherapy vs placebo plus chemotherapy</td>
<td>12.4 months vs 9.8 months</td>
<td>HR, 0.73; 95% CI, 0.62-0.86</td>
<td>( P &lt; .0001 )</td>
</tr>
<tr>
<td>CheckMate 649 (NCT02872116)</td>
<td>Unresectable, advanced, or metastatic gastric/GEJ/EAC with no known HER2 positivity</td>
<td>Nivolumab and ipilimumab, nivolumab and chemotherapy, or chemotherapy alone</td>
<td>13.8 months vs 11.6 months (nivolumab/chemotherapy vs chemotherapy)</td>
<td>HR, 0.77; 99.3%, 0.68-0.94</td>
<td>( P &lt; .0001 )</td>
</tr>
<tr>
<td>CheckMate 648 (NCT03143153)</td>
<td>Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma</td>
<td>Nivolumab/ipilimumab and nivolumab/chemotherapy vs chemotherapy alone</td>
<td>12.8 months to 10.7 months (nivolumab/ipilimumab vs chemotherapy)</td>
<td>HR, 0.78; 98.2% CI, 0.62-0.98</td>
<td>( P = .011 )</td>
</tr>
</tbody>
</table>

OS, overall survival; GEJ, gastroesophageal junction; EAC, esophageal adenocarcinoma.
were manageable. Based on these data, the FDA granted an accelerated approval in May 2021 to pembrolizumab in combination with trastuzumab and chemotherapy in this patient population.

BIOMARKERS IN CLINICAL PRACTICE
The current biomarkers validated for use in the clinical setting are the PD-L1 score, agnostic biomarkers such as mismatch repair or microsatellite instability (MMR/MSI), and tumor mutational burden (TMB). The PD-L1 CPS is the most common method of assessing PD-L1 expression in GEC. It is a qualitative immunohistochemistry assay where PD-L1 protein levels are detected in tumor tissues, and CPS was developed to consider the expression of PD-L1 on tumor cells and immune cells combined. Although CPS 10 appears to correlate to some degree with response to pembrolizumab, its utility is limited in PD-L1-negative tumors, and other biomarkers are needed.19

Mutations in genes encoding MMR and epigenetic silencing of MLH1 lead to an inability of cells to repair mismatched nucleotides during DNA replication, resulting in MMR deficiency. Consequently, this increases neoantigen burden and a heightened response to immune checkpoint inhibition in various tumors. MSI-H is a robust biomarker of immunotherapy response with predictability across various solid tumors and is approved as an agnostic biomarker for pembrolizumab. Nonetheless, a significant 40% to 60% proportion of patients with GEC who have MMR-deficient/MSI-high tumors still do not respond to immune checkpoint inhibitors, suggesting that there are additional immunosuppressive mechanisms in effect in the tumor microenvironment.19

TMB is another biomarker. High TMB is defined as at least 10 nonsynonymous somatic mutations per megabase of the tumor genome. In a phase 1/2 trial (NCT02915432) of toripalimab, a humanized PD-1 antibody, in patients with advanced gastric cancer who progressed on at least 1 prior systemic therapy, high TMB was associated with greater OS.20

NOVEL BIOMARKERS
Epstein-Barr virus (EBV) is a human herpesvirus associated with multiple cancer types such as lymphomas, nasopharyngeal carcinomas, and gastric adenocarcinomas. EBV-associated gastric cancers (EBVaGC) show intense intratumoral and peritumoral immune cell infiltration, making these tumors potentially more responsive to immune checkpoint blockade. However, the prevalence of EBVaGC is low in the Western population, and regular testing is not used for routine oncology care.21

Gene expression profiles can be used as biomarkers. For example, the KEYNOTE-059 study used a novel 18-gene T-cell–inflamed gene expression profiling score as a biomarker, whereas higher gene expression profiling score was associated with improved response.9 Our group used a targeted gene expression analysis in GEC to reveal that inflammation in the tumor-immune microenvironment is associated with improved OS in all patients. Furthermore, it was associated with improved OS and progression-free survival in patients treated with immune-modulating drugs.22 Tumor inflammation needs to be investigated further as a biomarker, perhaps in conjunction with other established biomarkers such as PD-L1.

Finally, circulating biomarkers, including circulating tumor DNA, which may be better reflective of the status of the tumor as compared with archival tissue-based biomarkers like PD-L1, should be evaluated in this context.

TAKE-HOME POINTS
Nivolumab is the new standard of care in the adjuvant setting for patients with esophageal/gastroesophageal junction cancers after chemoradiation therapy and surgery.

Chemoimmunotherapy is a potential new first-line treatment option for most patients with unresectable or metastatic gastroesophageal adenocarcinoma.

Some patients with advanced esophageal squamous cell carcinoma may be treated with combination immunotherapy based on CheckMate 648, pending FDA approval.

Biomarker selection will help us better identify patients suitable for immunotherapy.
1L aRCC treatment that
OFFERS A BALANCE OF DATA:
superior OS,* safety & tolerability, patient-reported quality of life1-6†

*vs sunitinib in patients with previously untreated aRCC.4
The primary endpoint was PFS (16.6 months with CABOMETYX + OPDIVO vs 8.3 months with sunitinib; HR=0.51; 95% CI: 0.41-0.64; P<0.0001). The secondary endpoints included OS (40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib; HR=0.60; 98.89% CI: 0.40-0.89; P=0.001; median OS was not reached in either arm), ORR, and safety.†

INDICATIONS
CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 or 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.
Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.
Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.
Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 57% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.
Diabetes: Diabetes occurred in 62% of CABOMETYX patients. Grade 3 diabetes occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiabetic medications as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.
Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.
Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom ≥1 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=15) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%) and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstituted treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for ONJ. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices.

Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for...
CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusa, abdominal pain, cough, and upper respiratory tract infection.

**DRUG INTERACTIONS**

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

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

**USE IN SPECIFIC POPULATIONS**

**Lactation:** Avoid women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

**Hepatic Impairment:** In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

**CheckMate-9ER study design**

A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety.1,3,4
With the combination of CABOMETYX and nivolumab, Grades 3 or 4 ALT or AST were seen in 11% of patients with ALT or AST > 3 times ULN (Grade 2+) were reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74% (89%). Among the 44 patients with Grade 2 ALT or AST who were rechallenged with either CABOMETYX (miv) or nivolumab (n11) as a single agent or both (n24), recurrence of Grade 2 increased ALT or AST was observed in 18 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

5.8 Adrenal Insufficiency
CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity. Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2/150) and Grade 4 (1/150). For Grade 2 adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC. Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 37% (4/11) of the 11 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency. 6 reinstated treatment after symptom improvement; of these, all (n6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 Proteinuria
Proteinuria was observed in 8% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

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

5.11 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing and safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

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

5.13 Thyroid Dysfunction
Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 15% of patients treated with CABOMETYX, including Grade 3 in 0% of patients. Patients should be assessed for signs of thyroid dysfunction prior to initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

5.14 Hypocalcemia
CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 3% of patients. Laboratory abnormality data were not collected in CABOSUN. In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients. Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

5.15 Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Caborzainlbnt administration to pregnant animals during organogenesis resulted in embryopathy/abnormalities at exposures below or close to the maximally achievable exposure, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR), 407 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), in 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), and in combination with nivolumab 240 mg/m² every 2 weeks in patients with RCC enrolled in a randomized, active-controlled trial (CHECKMate 826).

Withholding of CABOMETYX was observed in 70% of patients who discontinued CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients. Laboratory abnormality data were not collected in CABOSUN. In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients. Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

6.2 Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (7.2%)</td>
<td>31 (9.6%)</td>
<td>0.67</td>
<td>.012</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (0.9%)</td>
<td>13 (4.0%)</td>
<td>0.20</td>
<td>.16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (0.9%)</td>
<td>14 (4.3%)</td>
<td>0.25</td>
<td>.12</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (0.9%)</td>
<td>4 (1.2%)</td>
<td>0.70</td>
<td>.39</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (0.9%)</td>
<td>14 (4.3%)</td>
<td>0.25</td>
<td>.12</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (0.6%)</td>
<td>8 (2.5%)</td>
<td>0.41</td>
<td>.14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (7.2%)</td>
<td>31 (9.6%)</td>
<td>0.67</td>
<td>.012</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (0.9%)</td>
<td>13 (4.0%)</td>
<td>0.20</td>
<td>.16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (0.9%)</td>
<td>14 (4.3%)</td>
<td>0.25</td>
<td>.12</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (0.9%)</td>
<td>4 (1.2%)</td>
<td>0.70</td>
<td>.39</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (0.9%)</td>
<td>14 (4.3%)</td>
<td>0.25</td>
<td>.12</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (0.6%)</td>
<td>8 (2.5%)</td>
<td>0.41</td>
<td>.14</td>
</tr>
</tbody>
</table>

6.3 Metabolism and Nutrition

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>96 (28.9%)</td>
<td>87 (27.0%)</td>
<td>0.80</td>
<td>.60</td>
</tr>
</tbody>
</table>

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in > 2% of patients treated with CABOMETYX, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypocalcemia, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were: hypertension, diarrhea, fatigue, PPE, hypocalcemia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hyponatremia, and increased GGTP.

The dose was reduced in 62% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowered dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to treatment interruption occurred in 70% patients receiving CABOMETYX and in 58% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).
Other clinically important adverse reactions (all grades) that were reported in >1% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatic cholestasis (<1%).

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>74%</td>
<td>40%</td>
</tr>
<tr>
<td>Increased AL</td>
<td>65%</td>
<td>34%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>58%</td>
<td>7%</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>53%</td>
<td>43%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>48%</td>
<td>36%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>37%</td>
<td>26%</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>32%</td>
<td>28%</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>30%</td>
<td>21%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>29%</td>
<td>20%</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31%</td>
<td>21%</td>
</tr>
<tr>
<td>Anemia</td>
<td>31%</td>
<td>21%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td>ALP; alkaline phosphatase, ALT; alanine aminotransferase, AST, aspartate aminotransferase; GGT, gamma glutamyl transference. NO CTCAE Version 4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on laboratory abnormalities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily. All patients received 4 weeks on treatment followed by 2 weeks off, until disease progression or unacceptable toxicity. The median duration of treatment was 8.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥25%) in patients treated with CABOMETYX were hypertension, diarhoea, hyponatraemia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotenion, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 45% of patients receiving CABOMETYX and in 30% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=319)</th>
<th>Sunitinib (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>Percentage (%)</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>42%</td>
<td>6%</td>
</tr>
<tr>
<td>Rash*</td>
<td>23%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dryness</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>39%</td>
<td>16%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decrease</td>
<td>31%</td>
<td>12%</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>24%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>11%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidyndrom</td>
<td>21%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>14%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenna</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>28%</td>
<td>21%</td>
</tr>
<tr>
<td>Hypothyroidyndrom</td>
<td>5%</td>
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<tr>
<td>Angiopathy</td>
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<td>Investigations</td>
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</tr>
<tr>
<td>Increased ALT</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Increased blood creatinine*</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia*</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Confusional stasiion</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung infection</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Adverse reaction incidence details (percentages) are based on the number of patients who received each treatment (CABOMETYX or Sunitinib).

Table 4. Adverse Reactions in ≥ 1% Patients Receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=78)</th>
<th>Nivolumab (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>Percentage (%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarhoea</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Stomatosis</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Hypophosphate*</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Increased blood creatinine*</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia*</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>Hypothyroidyndrom</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Angiopathy</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Increased blood creatinine*</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia*</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteria</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Confusional stasiion</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung infection</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>
leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were: PPE (2%), fatigue, decreased appetite (1%), diarrhea (1%), and nausea (1%).

### Table 6. Adverse Reactions Occurring in ≥25% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=467)</th>
<th>Placebo (n=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td></td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54 10 19 2</td>
<td>14 0 2</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 13 2</td>
<td>20 0 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 &lt;1 &lt;1 &lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13 2 2</td>
<td>8 0 0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10 6 3</td>
<td>8 3 0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 10 30 4</td>
<td>12 0 0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22 7 8 2</td>
<td>12 0 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 2 2 &lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (N=467)</th>
<th>Placebo (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td></td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>79 9.8 38 3.0</td>
<td>24 0.3 11 0.4</td>
</tr>
<tr>
<td>Increased AST</td>
<td>77 7.9 37 2.6</td>
<td>25 0.3 11 0.4</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>45 4.2 20 0.9</td>
<td>16 0.2 6 0.2</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>54 1.9 24 0.8</td>
<td>20 0.3 10 0.2</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>47 1.3 25 0.3</td>
<td>18 0.3 8 0.2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>45 3.4 44 1.7</td>
<td>16 0.2 6 0.2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>64 3.1 32 1.2</td>
<td>24 0.3 10 0.2</td>
</tr>
<tr>
<td>Increased lypase</td>
<td>41 10 34 8.8</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Increased alkaline</td>
<td>41 2.8 37 1.6</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>increased creatinine</td>
<td>39 1.3 42 0.6</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>35 4.7 27 1.7</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>26 0.8 14 0.4</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>42 6.6 45 10</td>
<td>24 0.3 10 0.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43 0.3 70 9.7</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>37 2.5 61 4.8</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>37 0.3 66 5.1</td>
<td>16 0.3 6 0.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 3.2 87 12</td>
<td>16 0.3 6 0.2</td>
</tr>
</tbody>
</table>

* Each test incidence is based on the number of patients who had baseline and at least one on-study laboratory measurement available.

### Table 9. Laboratory Abnormalities Occurring in ≥25% of CABOMETYX-Treated Patients in COSMIC-311

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (N=125)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td></td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LDH</td>
<td>64 8 29 2</td>
<td>16 0 3 0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>73 12 37 5</td>
<td>20 0 0 0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>73 24 46 19</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>51 5 12 2</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>51 5 12 2</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>15 2 9 0</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>54 10 16 1</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Increased hemoglobin</td>
<td>40 8 8 0</td>
<td>16 0 0 0</td>
</tr>
</tbody>
</table>

### Table 9. Laboratory Abnormalities Occurring in ≥25% of CABOMETYX-Treated Patients in COSMIC-311

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (N=125)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td></td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LDH</td>
<td>64 8 29 2</td>
<td>16 0 3 0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>73 12 37 5</td>
<td>20 0 0 0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>73 24 46 19</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>51 5 12 2</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>51 5 12 2</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>15 2 9 0</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>54 10 16 1</td>
<td>16 0 0 0</td>
</tr>
<tr>
<td>Increased hemoglobin</td>
<td>40 8 8 0</td>
<td>16 0 0 0</td>
</tr>
</tbody>
</table>

* Each laboratory abnormality with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4) and NCI CTCAE Version 4.0

* Includes the following terms: mucosal inflammation, stomatitis

* Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

### Table 10. Laboratory Values Worsening from Baseline

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td>Grading</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 3.2 67 12</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>37 0.3 66 5.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>37 2.5 61 4.8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>37 0.3 66 5.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 3.2 87 12</td>
</tr>
</tbody>
</table>

* Includes productive cough.

* Includes primary hypothyroidism.

* Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

* Includes gastrointestinal reflux disease.

* Includes hypothyroidism.

* Includes hepatocellular aspartate, hepatocellular alanine aminotransferase increased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug induced liver injury, hepatic encephalopathy, hepatic steatosis, hepatic steatosis, hepatic steatohepatitis, intramuscular hemorrhage, increased hepatic transaminases increased, increased hepatic transaminases, hepatic hemorrhage.

* Includes musculoskeletal disorder, myalgia, neck pain, pain in extremity, spinal pain.

* Includes nasopharyngitis, pharyngitis, mints

### Table 11. Toxicity

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Toxicity</th>
<th>Daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>100%</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20%</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>Nausea</td>
<td>50%</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
<td>30 mg daily</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40%</td>
<td>40 mg daily</td>
</tr>
</tbody>
</table>

* Toxicity was graded per NCI CTCAE v4.
8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicity studies administration of cabozantinib to pregnant rabbits and rabbits during organogenesis resulted in embryolethality and structural abnormalities at exposures that were below those occurring clinically at the recommended dose (see Data). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve (AUC) at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose). In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose). In a pre-and postnatal study in rats, cabozantinib was administered from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

8.3.1 Pregnancy Testing

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

Contraception

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

Infertility

Females and Males

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

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Gestation Day 10 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg based on body surface area). Hypocalcemia was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner’s gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tumor abnormalities and thinning as well as effects on bones including reduced bone mineral content and density, puffy hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

CABOMETYX is not recommended for patients aged 65 years or older with DTC when CABOMETYX was aged 65 years or older, and 8% were 75 years or older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were aged 65 years and older, and 12% were 75 years and older. No overall differences in safety or effectiveness were observed in patients aged 65 years or older compared to younger patients with DTC.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with mild renal impairment. No dosage adjustment is recommended for patients with mild renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

8.7 Renal Impairment

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

8.8 Overdose

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

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to report any unusual bleeding or bruising and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their healthcare provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

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

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

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for pruritus or itchy rash.

Hypothyroidism: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

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

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoen cephalopathy syndrome: Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.

Embryo-fetal toxicity:

• Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.

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

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John’s wort.

Important administration information:

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.
EARLY EFFICACY DATA IN a phase 1 trial of the agent now known as nivolumab (Opdivo) were not enough to convince Julie Brahmer, MD, MSc, about the potential of the investigative agent. It was only when patients with non–small cell lung cancer (NSCLC) continued responding in readouts from the phase 2 trial that she was sure she was working on something important, an intuition confirmed by the results from the phase 3 CheckMate 057 trial (NCT01673867) and subsequent approval of the PD-1 inhibitor.

Brahmer, who is codirector of the Upper Aerodigestive Cancer Department at Johns Hopkins Medicine’s Bloomberg~Kimmel Institute for Cancer Immunotherapy in Baltimore, Maryland, has remained at the cutting edge of immunotherapy research and lung cancer treatment ever since. She has worked on dozens of trials and authored or coauthored nearly 200 papers, all while continuing to see patients in clinical practice.

Brahmer is also a cochair of the 19th Annual Winter Lung Cancer Conference®, which will take place February 4-6, 2022, virtually and on site at the Eden Roc Miami Beach hotel in Florida. The 3-day event hosted by Physicians’ Education Resource® (PER®), LLC, will provide a practical overview of recent advances in the landscape of lung cancer treatment.

During the conference, experts will discuss trial results that have changed or have the potential to change standards of care. Leaders in thoracic oncology joining Brahmer include cochairs Rogerio C. Lilenbaum, MD, director of Banner MD Anderson Cancer Center in Phoenix, Arizona, and Mark A. Socinski, MD, executive medical director at AdventHealth Cancer Institute in Orlando, Florida.

Faculty will discuss a wide range of recently published data from ongoing trials, debate controversial topics via Medical Crossfire® exchanges, and open the floor to discussions that address practical strategies for treating complex clinical cases. Topics of interest include:

• integrating and optimization of molecular testing throughout the continuum of disease,
• leveraging the growing therapeutic armamentarium for oncogene-driven NSCLC,
• applying consolidation immunotherapy in locally advanced NSCLC, and
• using surgery and radiation oncology for patients with thoracic malignancies.

Brahmer recently sat down for an interview with OncologyLive® to preview the conference in greater depth, share her thoughts about the major trends in lung cancer, and discuss some of the major work she has done over the course of her career. "This is a very exciting time in lung cancer care," she said. "A number of significant trial results have appeared in the past year or so, and a large number of very interesting trials are under way."

ONGOING RESEARCH SPARKS NEW DIRECTIONS IN CARE

Expanding PD-L1 inhibitors beyond expression

Among the most important results presented this year came from the phase 3 IMpower010 trial (NCT02486718), which supported the decision by the FDA to expand the approval of the PD-L1 inhibitor atezolizumab (Tecentriq).
The agent’s indication now includes the adjuvant treatment of patients with stage II to IIIA NSCLC, whose tumors express PD-L1 following surgery and platinum-based chemotherapy. The approval is the first adjuvant indication in NSCLC for an immunotherapy. The FDA also approved the VENTANA PD-L1 (SP263) Assay for use as a companion diagnostic device.

Data presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting in June and the European Society for Medical Oncology Annual Congress 2021 in September showed that the end point of disease-free survival (DFS) was met in the all-randomized stage II to IIIA population with a benefit demonstrated for those with PD-L1 expression of at least 1%.4,5

For those in the all-randomized stage II to IIIA population, at a median follow-up of 32.2 months (range, 0-57.5), the median DFS in patients who received atezolizumab (n = 442) was 42.3 months (95% CI, 36.0-not estimable [NE]) vs 35.3 months (95% CI, 30.4-46.4) in patients who received best supportive care (n = 440; HR, 0.79; 95% CI, 0.64-0.96; P = .02). The 36-month DFS rates were 55.7% vs 49.4%, respectively.

At a median follow-up of 32.8 months (range, 0.1-57.5), the median DFS for patients with PD-L1 expression of at least 1% on tumor cells who received atezolizumab (n = 248) was NE (95% CI, 36.1-NE) vs 35.8 months (95% CI, 29.0-NE) for those who received best supportive care (n = 228; HR, 0.66; 95% CI, 0.50-0.88; P = .004).

Atezolizumab performed particularly well in patients with high PD-L1 expression. In a prespecified secondary subgroup analysis of patients with stage II to IIIA NSCLC with a PD-L1 tumor cell expression of 50% or higher (n = 229), the HR for DFS vs best supportive care was 0.43 (95% CI, 0.27-0.68). In results of an exploratory analysis, patients with a PD-L1 tumor cell expression ranging from 1% to 49% (n = 247), the HR for DFS was 0.87 (95% CI, 0.60-1.26).5

The most frequently reported adverse effects were increased aspartate aminotransferase, increased blood creatinine, and increased alanine aminotransferase. Other toxicities included hyperkalemia, rash, cough, hypothyroidism, pyrexia, fatigue/asthenia, musculoskeletal pain, peripheral neuropathy, arthralgia, and pruritus. The recommended atezolizumab dose for this indication is 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks.

“PD-L1 expression can be a biomarker for a treatment decision and can also help us think about the best treatment for a given person,” Brahmer said. “In patients with stage II to IIIA disease, we’ve seen that an immunotherapy with atezolizumab can be beneficial.”

KRAS G12C

Atezolizumab was not the only drug to earn an FDA approval for NSCLC, and Brahmer thinks it will be interesting to see if the drug is adopted quickly on the strength of the trial results, said. “It’s early on, but the data we’re seeing show increased chances of cure or at least increased disease-free survival in these patients with early-stage disease.”

KRAS G12C

Sotorasib is the first drug approved for patients with KRAS G12C mutation in NSCLC, and Brahmer thinks it will be interesting to see if the targeted drug will be used in such patients relative to other treatment options.

“Right now, at least in patients with driver-mutated tumors who are never smokers, we typically start with the tyrosine kinase inhibitor [TKI],” she said. “Where it gets a little bit harder right now is in patients with KRAS G12C inhibitors, where immune checkpoint inhibitors as a single agent have a decent response rate, somewhere between 30% and 40%. That is where we need head-to-head comparison studies to see what is best to give these patients first,” said Brahmer, who added that there are reasons beyond treatment efficacy to prefer trying TKIs before immunotherapy.

“A lot of us are a bit hesitant when we’re giving immunotherapy first in patients who will receive TKIs next because there’s concern about increased adverse effects. It takes [time] for the immunotherapy antibody to get out of [the patient’s] system, and the effects on a patient’s immune system can last for months to years. Sometimes when we add a TKI to immunotherapy or start a TKI after immunotherapy, we can see more unusual adverse effects or increased adverse effects, and that’s always a concern.”

“It’s gratifying to know that I played a small part in the development of this thing that has extended so many lives among patients who did not have many treatment options until then.”

—JULIE BRAHMER, MD, MSc

In published findings from CodeBreak 100, sotorasib elicited an objective response rate (ORR) of 37.1% (95% CI, 28.6%-46.2%) among 124 patients with KRAS G12C-mutated NSCLC who had progressed following treatment with an immunotherapy and/or chemotherapy. The median duration of response (DOR) with the treatment was 11.1 months (95% CI, 6.9-NE), and the disease control rate was 80.6% (95% CI, 72.6%-87.2%).7 The median progression-free survival (PFS) was 6.8 months (95% CI, 5.1-8.2), and the median overall survival (OS) was 12.5 months (95% CI, 10.0-NE).

Findings from exploratory biomarker analyses revealed that sotorasib demonstrated clinical activity across a range of biomarker subsets, including those with PD-L1-negative or -low status, and those with tumors that exhibited STK11 mutations.8

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Adverse Effects Come Into Focus
Managing adverse effects from immunotherapy will be a major point of emphasis at the conference because strategies for treatment selection and toxicity management continue to evolve.

“For the most part, oncologists are now getting comfortable treating patients on with this class of medication, but there are always nuances in dealing with the toxicities,” Brahmer said. “The guidelines help give us a framework to treat or mitigate the adverse effects, and we’ll discuss those. I also think we’re learning more about who we can safely treat and how to best use these therapies in patients with preexisting autoimmune diseases as well. At the conference, we hope to focus on some complex cases that we see occasionally in the clinic to give the providers in attendance a framework in thinking about these toxicities.”

MOLECULAR TESTING SOLIDIFIES ROLE IN NSCLC
Another area of emphasis at the conference will be strategies for using molecular tests to guide caregiver decisions, both before treatment and as treatment continues. The number of molecular tests has ballooned in recent years along with the number of medications targeted at new mutations.

This year, for example, the FDA approved 2 diagnostic tests designed to evaluate eligibility for 2 novel agents—amivantamab-vmjw (Rybrevant) and mobocertinib (Exkivity)—both of which were approved for patients with NSCLC with EGFR exon 20 insertion mutations (TABLE). They are the first treatments for these rare mutations, which are associated with aggressive cancer growth.

The amivantamab approval—which was joined by an approval for a companion diagnostic, the Guardant360 CDx liquid biopsy assay and the QIAGEN therascreen KRAS RQG PCR kit—was based on data from the phase 1 CHRYSALIS trial (NCT02609776). Results showed that amivantamab elicited an ORR of 40% (95% CI, 29%-51%) among 81 pretreated patients whose NSCLC had EGFR exon 20 insertion mutations. The median DOR was 11.1 months (95% CI, 6.9-NR) with 63% of responders maintaining a response for at least 6 months.

Among those who responded to amivantamab, 3 achieved complete response and 29 had partial responses. Variations in EGFR exon insertion mutations that were detectable in circulating tumor DNA did not seem to affect response to treatment. The median PFS for patients who received amivantamab was 8.3 months (95% CI, 6.5-10.9), and the median OS was 22.8 months (95% CI, 14.6-NR).

Almost all participants experienced treatment-related adverse effects (TRAEs). Some 16% experienced TRAEs that were grade 3 or higher, 9% percent of patients reported serious TRAEs, and 4% had toxicities that resulted in discontinuation.

The mobocertinib approval—which also came with the approval of a companion diagnostic, Thermo Fisher Scientific’s Oncomine Dx Target Test—was based on results from a phase 1/2 trial (NCT02716116) on a cohort of 114 patients with EGFR exon 20 insertion-positive NSCLC who had received prior platinum-based therapy.

Results showed that mobocertinib elicited an ORR of 28% (95% CI, 20%-37%) and a DOR of 17.5 months (95% CI, 7.4-20.3). The median PFS was 7.3 months (95% CI, 5.5-9.2), and the median OS was 24.0 months (95% CI, 14.6-28.8). Further, the ORR in the cohort of patients who received prior platinum-based therapy was 35% (95% CI, 26%-45%) with a median DOR of 11.2 months (95% CI, 5.6-NE). The confirmed disease control rate in this cohort per investigator assessment was 78% (95% CI, 69%-85%).

The most common TRAEs included diarrhea, rash, nausea, stomatitis, vomiting, and decreased appetite. The prescribing information for mobocertinib includes a box warning for heart-rate corrected QT prolongation and torsades de pointes, in addition to warnings and precautions for interstitial lung disease/pneumonitis, cardiac toxicity, and diarrhea.

TABLE. Approval Snapshot

<table>
<thead>
<tr>
<th>Amivantamab-vmjw (Rybrevant)</th>
<th>Approval date: May 21, 2021</th>
<th>Trial for efficacy: CHRYSALIS (NCT02609776)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Companion diagnostics: QIAGEN therascreen KRAS RQG PCR kit (QIAGEN GmbH) and Guardant360 CDx (Guardant Health)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Prior platinum-based chemotherapy (n = 81)</td>
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</tr>
<tr>
<td>ORR (95% CI)</td>
<td>40% (29%-51%)</td>
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</tr>
<tr>
<td>CR</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>11.1 (6.9-NE)</td>
<td></td>
</tr>
<tr>
<td>DOR ≥ 6 months</td>
<td>63%</td>
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<tr>
<td>AEs ≥20%: rash, infusion-related reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mobocertinib (Exkivity)</th>
<th>Approval date: September 15, 2021</th>
<th>Trial for efficacy: AP32788-15-101 (NCT02716116)</th>
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<tbody>
<tr>
<td>Companion diagnostic: Oncomine Dx Target Test (Life Technologies Corporation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Mobocertinib (n = 114)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>28% (20%-37%)</td>
<td></td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>17.5 (7.4-20.3)</td>
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</tr>
<tr>
<td>DOR ≥ 6 months</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>AEs ≥20%: diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Box warning: QTc prolongation and Torsades de pointes: Monitor heart-rate corrected QT (QTc) and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation. Avoid use of concomitant drugs that are known to prolong the QTc interval. Avoid use of strong or moderate CYP3A inhibitors that may further prolong QTc. Withhold, reduce the dose, or permanently discontinue mobocertinib based on the severity.

AE, adverse effect; CR, complete response; DOR, duration of response; NE, not estimable; NSCLC, non–small cell lung cancer; ORR, overall response rate; PR, partial response.
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• Watch the experts tackle the latest controversies in lung cancer in dynamic Medical Crossfire® exchanges
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“We’ll certainly be going over all of these new inhibitors that are being approved by the FDA on what almost seems like a monthly basis, focusing on some of the new FDA approvals for KRAS G12C mutations, EGFR exon 20 mutations, as well as HER2 mutations,” Brahmer said. “I’m excited to be able to offer [participants] a time to discuss some of these new treatment options and to figure out how best to integrate them into practice.”

As Brahmer spoke of the new targeted agents, she returned to the topic of molecular testing. “As targetable mutations proliferate, testing obviously becomes more important, so we want to go over testing: who to test, what tests are best,” Brahmer said. “In the metastatic setting, we always struggled with the issue of getting enough tumor tissue and in trying to get those results as quickly as possible so that we can get the patients on the right treatment as quickly as possible. Certainly, we do use blood-based cell-free DNA testing platforms in order to try to get those results more quickly.”

TRIUMPH IN A CAREER PASSION

Brahmer grew up in rural Nebraska, the daughter of a sixth-generation farmer and a nurse. She became interested in oncology during her high school years, after her grandfather died of lymphoma. After completing her undergraduate degree at Creighton University in Omaha, she graduated from the University of Nebraska Medical School, where she conducted her first cancer research under the tutelage of Julie Vose, MD, MBA, a past president of ASCO.

After serving her internship and residency at The University of Utah in Salt Lake City, Brahmer accepted an oncology/hematology fellowship at Johns Hopkins Medicine, where she has remained. “I specifically got interested in lung cancer at Johns Hopkins after meeting David S. Ettinger, MD, who is a giant in our field,” Brahmer said. “He opened my eyes to the opportunities and the need for research in lung cancer back in 2000, and I’ve been in this field ever since, blessed to have amazing mentors and colleagues.”

Among Brahmer’s interests were early-stage trials, often first-in-human uses for potential lung cancer treatments. The overwhelming majority of these agents never went beyond the tiny preliminary trials, and even those that showed some early promise tended to fizzle out, which was why Brahmer controlled her enthusiasm when she saw strong responses in that first nivolumab trial. Still, there was a part of her that thought she might be involved with something important.

“I had been the principal investigator on a lot of phase 1, first-in-human trials that just never went anywhere,” she said. “So even the phase 1 trial was exciting because in patients who responded well the disease would just melt away and not come back for months or years.” Brahmer added that many observers were so sure immunotherapy would not work for lung cancer that they assumed these early trial results were coincidences.

“That feeling continued among the oncology community as a whole until the phase 3 study, and even at that point, a lot of [practitioners] still felt it was a fluke,” Brahmer said. “So now, all these years later, seeing that there are groups of patients within lung cancer—as well as in other cancers—benefitting from these treatments, it’s very exciting and gratifying. It’s gratifying to know that I played a small part in the development of this thing that has extended so many lives among patients who did not have many treatment options till then.”

Brahmer has continued to study the use of immunotherapies in lung cancer treatment, and she and other investigators have made many discoveries over those years that have increased the benefits of such medications. Still, many questions remain unanswered.

“We’d really like to learn to predict who can get away with receiving just single-agent immunotherapy and just keep on responding. We’d basically need tests that are as accurate as the ones we have for driver mutations, tests that would allow us to do precision immunotherapy. We’re not there yet, but we’re making progress,” Brahmer said. “We’re also getting a better idea of which combinations which patients should receive. There’s obviously a bunch of different potential combinations, checkpoint inhibitors being tested with cellular therapies. We also want to learn more about predicting which patients still need to rely on chemotherapy to get their disease under control, and we are making steps toward figuring that out. Short term, I think we’ll learn more about how best to sequence treatments. Should we be giving everything up front to these patients to give their best chance of response? If we do, does that affect their long-term disease control? The list of questions is long, but we’re making progress on many fronts. It’s a very rewarding time to be in cancer research.”

For a full list of references, see the article at OneLive.com.
More From Julie Brahmer, MD, MSc

Trials Needed to Determine Role for Targeted Therapies in Locally Advanced NSCLC

by Jessica Hergert

Although Adjuvant Treatment with durvalumab (Imfinzi) after chemoradiation has advanced the management of patients with unresectable stage III non–small cell lung cancer (NSCLC), the lack of benefit observed in patients with EGFR mutations underscores the need to develop clinical trials to determine whether patients with oncogene-driven locally advanced disease should receive immunotherapy or targeted therapy, said Julie Brahmer, MD, MSc.

In an interview with OncologyLive® during the 16th Annual New York Lung Cancers Symposium®, a program hosted by Physicians’ Education Resource® (PER®), LLC, Brahmer discussed remaining questions regarding immunotherapy and targeted therapy in locally advanced NSCLC, data from the phase 3 PACIFIC (NCT02125461) and ADAURA (NCT02511106) trials, and her hopes for future clinical trials in the paradigm.

How do the results of the PACIFIC trial inform treatment decisions for patients with NSCLC?
In the PACIFIC study, durvalumab improved overall survival (OS) in general for patients with NSCLC after concurrent chemoradiation. Although there wasn’t a huge number of patients with EGFR mutations, the data clearly showed that durvalumab did not seem to improve progression-free survival (PFS) or OS in that small patient group.

Many of us will not automatically give [patients with EGFR mutations] durvalumab in the consolidative setting because we know these patients have a high likelihood of progression. If we start tyrosine kinase inhibitors [TKIs] shortly after immunotherapy, we may run into issues with toxicity, much more so than if we started with TKIs alone in the stage IV setting.

We are trying to extrapolate from advanced disease where we know that single-agent immunotherapy does not work at all for patients with EGFR, ALK, ROS1, HER2, or RET mutations. The jury is out for patients with KRAS or BRAF mutations where single-agent immunotherapy in advanced disease works quite well. Data support the use of single-agent immunotherapy in BRAF V600E-mutated disease in the metastatic setting; however, the jury is out for patients after concurrent chemoradiation. We don’t have that information, but we need it if we are truly going to deliver precision oncology.

What is known about osimertinib’s [Tagrisso] role after concurrent chemoradiation?
With the data from the ADAURA trial showing a significant improvement in disease-free survival [DFS] with osimertinib after adjuvant chemotherapy, we need to go back and look at osimertinib after chemoradiation. We saw data that turned us off initially to using concurrent chemoradiation followed by docetaxel and gefitinib [Iressa]. Patients who received gefitinib did poorly, but this was in a general patient population. We need to drill down to patients with specific mutations to try TKIs after definitive therapy.

A study out of Japan [UMIN000008366] was recently presented looking at gefitinib with concurrent thoracic radiation therapy in locally advanced, EGFR-mutated NSCLC. The response rate was quite high at 81.5% with the combination. The median OS was 61.1 months. [The results didn’t show] a significant problem with pneumonitis or other toxicities, but it was a relatively small study.

We have some retrospective studies from different institutions looking at EGFR-mutant stage III disease. It seems that the survival is much better in those patients who received EGFR TKIs after concurrent chemoradiation compared with that same population receiving durvalumab vs a TKI.

Regarding immunotherapy in unresectable stage III disease, consolidation durvalumab does not seem to benefit patients with EGFR mutations. However, there are limited data in this setting [to determine] what the best [treatment] to give these patients is. Plus, if we extrapolate data from stage IV disease, single-agent immunotherapy does not seem active, and it certainly adds toxicity when we start TKIs.

In patients with EGFR-mutant disease, adjuvant osimertinib does improve DFS. We need a study to look at this in the locally advanced setting after definitive therapy. We have mixed results, but if we look at a specific group of oncogene-driven disease, we could do a study on this.

There is a black hole with no data in patients with other oncogene-driven NSCLC. This is an area where we need to bring precision oncology to the locally advanced setting.

What barriers must be overcome to ensure patients who are eligible for targeted therapy receive it?
In patients with nonsquamous histology or patients who are never smokers that come in with other histologies, trying to get testing performed can be a barrier all the way from making sure we have enough tissue. If tissue is the issue, being able to get on top of things right away with a liquid biopsy in patients with advanced disease is important. However, trying to figure out how to time [liquid biopsies is challenging].

For patients, insurance issues can arise when companies are billed for a liquid and tissue biopsy. This can become burdensome and complicated for patients as some insurance companies only cover 1 [test]. Making sure that patients’ insurance covers the mutation testing from a particular company adds another layer of complexity to the situation.

Additionally, we don’t have the time that mutation testing takes. Certainly, if [the patients fall into] the 70% of patients where we can detect tumor DNA in their blood, blood-based testing significantly shortens the time [required for genetic testing].

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**INDICATION**

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

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

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Infusion-Related Reactions**

RYBREVANT\textsuperscript{\textregistered} can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

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

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

**Interstitial Lung Disease/Pneumonitis**

RYBREVANT\textsuperscript{\textregistered} can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT\textsuperscript{\textregistered}, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT\textsuperscript{\textregistered} due to ILD/pneumonitis.

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

**Dermatologic Adverse Reactions**

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

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT\textsuperscript{\textregistered}.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT\textsuperscript{\textregistered}. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
In a multicenter, open-label, multicohort study\(^1\)*

**Results for tough-to-treat disease**

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

- Efficacy was evaluated by ORR\(^1\) and DOR\(^1\)

\(^*\)CHRYSLIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBREVANT\(^\text{®}\) in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR exon 20 insertion mutations as detected by an FDA-approved test, whose disease had progressed on or after platinum-based chemotherapy. RYBREVANT\(^\text{®}\) was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.\(^1\)

\(^1\)According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).\(^1\)

\(^*\)Based on Kaplan-Meier estimates.\(^1\)

**The safety of RYBREVANT\(^\text{®}\) was evaluated in the CHRYSLIS\(^*\) study (n=129)\(^1\):**

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity\(^1\)
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).\(^1\)

- IRRs occurred in 66% of patients treated with RYBREVANT\(^\text{®}\), the majority of which may occur with the first infusion.\(^1\)

\(^1\)Based on the safety population, N=302.

CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non–small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT\(^\text{®}\) based on severity.

**Ocular Toxicity**

RYBREVANT\(^\text{®}\) can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT\(^\text{®}\). All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT\(^\text{®}\) based on severity.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and findings from animal models, RYBREVANT\(^\text{®}\) can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT\(^\text{®}\).

**Adverse Reactions**

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

Please see Brief Summary of full Prescribing Information for RYBREVANT\(^\text{®}\) on subsequent pages.

**References:**

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**INDICATIONS AND USAGE**

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

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

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Infusion-Related Reactions**

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

Based on the safety population [see Adverse Reactions], IRR occurred in 68% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended [see Dosage and Administration (2.3) in Full Prescribing Information]. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.6) in Full Prescribing Information].

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

**Interstitial Lung Disease/Pneumonitis**

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

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

**Dermatologic Adverse Reactions**

RYBREVANT can cause rash (including dermatitis acneiform), pruritus, and dry skin. Based on the safety population [see Adverse Reactions], rash occurred in 74% of patients treated with RYBREVANT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 2 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients [see Adverse Reactions].

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

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

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

**Ocular Toxicity**

RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population [see Adverse Reactions], keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

**Embryo-Fetal Toxicity**

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

**ADVERSE REACTIONS**

The following adverse reactions are discussed elsewhere in the labeling:

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

**Clinical Trials Experience**

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

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

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

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had ≥ 12% were exposed for greater than one year.

Successful adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

**Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death. Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 99% of patients. Adverse reactions requiring dose interruption in ≥25% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

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

The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.
Table 1 summarizes the adverse reactions in CHRYSALIS.

Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVANT+ (N=129)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>84</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>33</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Edema*</td>
<td>27</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>47</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>37</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>26</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain*</td>
<td>11</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Headache*</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Table 2 summarizes the laboratory abnormalities in CHRYSALIS.

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

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

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

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

In CHRYSALIS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

**Data**

**Animal Data**

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

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

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

**Pregnancy Testing**

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

**Contraception**

**Females**

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

**Pediatric Use**

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

**Geriatric Use**

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

**PATIENT COUNSELING INFORMATION**

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

**Infusion-Related Reactions**

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

**Interstitial Lung Disease/Pneumonitis**

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

**Dermatologic Adverse Reactions**

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

**Ocular Toxicity**

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

**Paronychia**

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

**Embryo-Fetal Toxicity**

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

**Lactation**

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

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Overcoming Mechanisms of Resistance Remains at the Forefront for EGFR-Mutant NSCLC

by COURTNEY MARABELLA

ALTHOUGH NEXT-GENERATION TYROSINE kinase inhibitors (TKIs) such as osimertinib (Tagrisso) have helped to overcome resistance in EGFR-mutated non-small cell lung cancer (NSCLC), a more complete understanding of resistance mechanisms will pave the way for further advances for patients with this disease, according to Roy S. Herbst, MD, PhD.¹

“Everyone with an EGFR mutation gets an EGFR inhibitor, and we are moving them to the earliest setting,” Herbst, the Ensign Professor of Medicine, professor of pharmacology, director of Center for Thoracic Cancers, and chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital in New Haven, Connecticut, said during his presentation at the 16th Annual New York Lung Cancers Symposium®. “There are a multitude of resistance mechanisms, and personalized therapy upon resistance is probably going to be the norm going forward.”

Biopsy, either liquid or tissue, remains an important part of care for patients with EGFR-mutant disease because it helps detect actionable mechanisms of resistance.

Furthermore, similar strategies may help overcome resistance to targeted therapy in other oncogene-driven lung cancers, Herbst noted.

OSIMERTINIB MOVES TO THE FRONT LINE

EGFR TKIs began to be studied in the 1990s, with first-generation drugs such as gefitinib (Iressa) and erlotinib (Tarceva) introduced as treatment options. These were followed by second-generation agents such as afatinib (Gilotrif) and dacomitinib (Vizimpro), and then the third-generation EGFR TKI osimertinib. According to the results of the phase 2 AURA2 trial (NCT02094261), osimertinib showed activity in patients with EGFR T790M-mutant NSCLC, with an overall response rate (ORR) of 62% (95% CI, 54%-68%), and a disease control rate (DCR) of 90% (95% CI, 85%-94%) among 198 evaluable patients.²

Data from the phase 3 FLAURA trial (NCT02296125) established the agent as the standard of care for first-line treatment for this patient population in the United States and Europe. The study enrolled patients 18 years or older with a World Health Organization (WHO) performance status of 0 or 1, exon 19 deletion- or L858R-positive disease, and no prior systemic anticancer or EGFR TKI treatment. Those with stable central nervous system (CNS) metastases were eligible to enroll.

Patients were randomized 1:1 to receive either osimertinib or gefitinib or erlotinib every 6 weeks until objective progressive disease. Patients were stratified by mutational status (exon 19 deletion or L858R), and race (Asian or non-Asian), and crossover was allowed for patients in the gefitinib or erlotinib arm who could receive open-label osimertinib upon central confirmation of progression and T790M positivity.³

The primary end point of the study was investigator-assessed progression-free survival (PFS), and secondary end points included ORR, duration of response, DCR, depth of response, overall survival (OS), patient-reported outcomes, and safety.

Results showed that the median PFS in the osimertinib arm was 18.9 months (95% CI, 15.2-21.4) vs 10.2 months (95% CI, 9.6-11.1) in the gefitinib or erlotinib arm, which led to the FDA approving the
The significant benefit demonstrated by EGFR TKIs in those with EGFR-mutant advanced NSCLC provided rationale for testing these agents in patients with early-stage disease, according to Herbst. Surgery and adjuvant cisplatin-based chemotherapy are the recommended treatment strategies for those with stage II to IIIA disease, as well as select patients with stage IB disease. However, rates of disease recurrence and death following these treatment strategies remain high across stages. Similarly, the prevalence of EGFR mutations appears similar across disease stages.4

“If EGFR TKIs were available in the resectable setting, a similar proportion of patients may be able to benefit compared with the advanced setting,” Herbst said. Investigators tested this hypothesis in the phase 3 ADAURA trial (NCT02511106), which examined osimertinib in patients with completely resected stage IB, II, or IIIA NSCLC, with or without adjuvant chemotherapy. The study enrolled those 18 years or older with a WHO performance status of 0 or 1 and confirmed primary nonsquamous NSCLC with exon 19 deletions or L858R positivity. Brain imaging was required, if not completed preoperatively, as well as complete resection with negative margins. The maximum interval between surgery and randomization was 10 weeks for those without adjuvant chemotherapy and 26 weeks for those with adjuvant chemotherapy.3

Patients were stratified by disease stage, EGFR mutation status, and race. They were randomized 1:1 to received either daily osimertinib or placebo. The planned treatment duration was 3 years, and treatment continued until recurrence, completion, or discontinuation.

The primary end point of the study was disease-free survival (DFS) in patients with stage II/IIIA disease, and secondary end points included DFS in the overall population; DFS at 2, 3, and 5 years; OS; and safety.

Results showed that osimertinib improved DFS in patients with stage II/IIIA disease, with the median DFS not reached (NR; 95% CI, 38.8-not calculable [NC]) vs 19.6 months (95% CI, 16.6-24.5) with placebo. Additionally, the median DFS was not reached in the overall population (95% CI, NC-NC) with osimertinib vs 27.5 months (95% CI, 22.0-35.0) with placebo.

When broken down by stage, the 2-year DFS rate for those in the osimertinib arm was 87% (95% CI, 77%-93%) for those with stage IB disease, 91% (95% CI, 82%-95%) for those with stage II disease, and 88% (95% CI, 79%-94%) for those with stage IIIA disease, compared with 73% (95% CI, 62%-81%), 56% (95% CI, 45%-65%), and 32% (95% CI, 23%-42%) for placebo, respectively (TABLE).4

Investigators also evaluated additional considerations beyond the study treatment including local vs distant recurrence, sites of disease recurrence, incidence of CNS metastases, subsequent therapies, and quality of life, Herbst said.

For those with resected NSCLC, the type of recurrence is a key consideration, as local vs distant recurrence affects postsurgery outcomes. For example, local/regional recurrence is associated with longer survival post recurrence compared with distant recurrence.6,7 Moreover, because CNS is a common site of metastases among those with EGFR-mutant NSCLC receiving EGFR TKIs, preventing recurrence in the CNS is a significant unmet need.8

Data from the ADAURA trial showed that 11% of patients on the osimertinib arm experienced disease progression or death vs 46% on the placebo arm. Additionally, a majority of those who experienced recurrence on the osimertinib arm had local/regional recurrence, with 38% experiencing metastatic recurrence vs 61% on the placebo arm. The most common sites of recurrence in the osimertinib and placebo arms included the lungs (6% vs 18%, respectively), lymph nodes (3% vs 14%), and CNS (1% vs 10%).

**TABLE. 2-year DFS Rates by Disease Stage in the ADAURA Trial**

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Osimertinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB (95% CI)</td>
<td>87% (77%-93%)</td>
<td>73% (62%-81%)</td>
</tr>
<tr>
<td>Stage II (95% CI)</td>
<td>91% (82%-95%)</td>
<td>56% (45%-65%)</td>
</tr>
<tr>
<td>Stage IIIA (95% CI)</td>
<td>88% (79%-94%)</td>
<td>32% (23%-42%)</td>
</tr>
</tbody>
</table>

DFS, disease-free survival.

Next Steps? Targeting Resistance

Several ongoing trials are examining osimertinib, such as the phase 3 NeoADAURA (NCT04351555) trial and the phase 3 LAURA trial (NCT03521154), and others are looking at combination strategies with osimertinib and different EGFR TKIs. However, one of the biggest areas of research going forward will be targeting mechanisms of resistance to these agents, Herbst says.

Mechanisms of acquired resistance to first- and second-generation TKIs include secondary mutations in the drug target, activation of bypass signaling pathways,

There are a multitude of resistance mechanisms, and personalized therapy upon resistance is probably going to be the norm going forward.”

—ROY S. HERBST, MD, PhD

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mutations in downstream pathways, and phenotypic changes in the tumor. For patients who are TKI naïve with an EGFR mutation and receive a first- or second-generation EGFR TKI, a physician would perform a biopsy upon progression to determine if the patient was T790M positive, in which case the patient would move on to osimertinib. After progression on osimertinib, a clinical trial would likely be recommended, according to Herbst. For those who are T790M negative after the repeated biopsy, a clinical trial would also be recommended, as well as for those who initially receive osimertinib and then develop resistance. Most (30%-40%) mechanisms of resistance to second-line osimertinib are largely unknown. Known mechanisms include acquired EGFR mutations (10%-26%), acquired amplifications (5%-50%), transformations (4%-15%), acquired cell cycle gene alterations (12%), acquired oncogenic fusions (3%-10%), and acquired MAPK-PI3K mutations (2%-10%). Similarly, mechanisms of resistance to first-line osimertinib are largely unknown (40%-50%). Known mechanisms include acquired EGFR mutations (6%-10%), acquired amplifications (8%-17%), transformations (15%), acquired cell cycle gene alterations (10%), acquired oncogenic fusions (1%-8%), and acquired MAPK-PI3K mutations (13%-14%). However, strategies for overcoming these mechanisms remain unclear.

“Patients will get a liquid biopsy or repeat tumor biopsy, we will figure out what is the mutation that they have, and perhaps we will know which drug to pull off the shelf, or which combination of drugs to use,” Herbst said. “I rarely will use immunotherapy in these patients, although if there is really nothing else to do, we have done it on very few occasions.”

REFERENCES

KRAS G12C Inhibitors Enter the Spotlight in NSCLC

by JASON HARRIS

THE ERA OF DIRECT INHIBITORS to treat KRAS G12C-mutated non–small cell lung cancer (NSCLC) has arrived in the clinic, said Gregory J. Riely, MD, PhD, said during his presentation at the 16th Annual New York Lung Cancers Symposium. Riely is vice chair of clinical research in the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York, New York.

In 2013 Sang Min Lim, PhD, and colleagues developed sotorasib (Lumakras) to specifically target KRAS G12C, what was once considered an undruggable target. Approximately 13% of patients with lung cancer harbor the mutation, which is also found in up to 3% of those with colorectal cancer and other solid tumors.

In May 2021, the FDA granted accelerated approval for sotorasib, an RAS GTPase family inhibitor, for adults with KRAS G12C–mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy. Data from the phase 2 CodeBreAk 100 trial (NCT03600883), which supported the decision, were published by Skoulidis et al in the New England Journal of Medicine in June 2021.

The findings showed that sotorasib elicited an objective response rate (ORR) of 36% (95% CI, 28%-45%) among 124 patients with KRAS G12C–mutated NSCLC who progressed following treatment with immunotherapy and/or chemotherapy. The median duration of response (DOR) with the treatment was 10 months, and 58% of patients experienced a DOR of 6 months or more.

The median progression-free survival (PFS) was 6.8 months, and the median overall survival (OS) was 12.5 months.

“Among the most impressive findings of the study were the durability and depth of responses, and it should be noted that 4 patients [3.2%] achieved a complete response,” Ferdinandos Skoulidis, MD, PhD, MRCP, an assistant professor of thoracic/head and neck medical oncology at The University of Texas MD Anderson Cancer Center in Houston, told OncologyLive® in August 2021. “The reported overall disease control rate [DCR] of 80.6% with median PFS of 6.8 months and median OS of...”
12.5 months further support the activity of sotorasib in this heavily pretreated patient population and appear superior to historical data with docetaxel or docetaxel and ramucirumab [Cyramza].”

Investigators enrolled 126 patients into the trial, 124 of whom had centrally evaluable lesions per RECIST 1.1 criteria at baseline. Eligible patients were required to have locally advanced or metastatic NSCLC with a KRAS G12C mutation, as assessed per central testing of tumor biopsies. Patients had to have progressed on prior standard therapies, and those with active brain metastases were excluded.

Patients were assigned to 960 mg of oral sotorasib daily until disease progression. Radiographic scans were done every 6 weeks for up to 48 weeks, and then once every 12 weeks thereafter.

The primary end point of the trial was ORR per RECIST 1.1 criteria by blinded independent central review, and key secondary end points included DOR, DCR, time to recovery, PFS, OS, and safety.

Twenty-eight (22.2%) patients experienced treatment-related adverse effects (TRAEs) requiring dose modifications, and 9 (7.1%) discontinued treatment due to TRAEs.

There were 20 (15.9%) grade 5 AEs, although investigators concluded none were related to treatment. Investigators recorded 26 grade 3/4 AEs, the most common of which was grade 3 alanine aminotransferase increase (n = 8).

Investigators are examining sotorasib vs docetaxel for the same patient population in the ongoing randomized phase 3 CodeBreak 200 trial (NCT04303780). The estimated study completion date is April 2026.

THE FUTURE OF KRAS G12C TARGETING

Sotorasib is the first KRAS inhibitor to win FDA approval, but other agents are sure to follow. In June 2021, the FDA granted a breakthrough therapy designation to adagrasib (MRTX849) as a potential therapeutic option for patients with KRAS G12C–mutated NSCLC following previous systemic therapy. Adagrasib is a covalent inhibitor that irreversibly and selectively binds KRAS G12C in its inactive guanosine diphosphate–bound state. The agent has been optimized for desired properties, demonstrating high selectivity for KRAS G12C mutations over wild type and favorable pharmacokinetic properties, including oral bioavailability, a half-life of approximately 24 hours, and extensive tissue distribution.

Pasi A. Jänne, MD, PhD, the 2021 Giants of Cancer Care® award winner for lung cancer, led the registrational phase 1/2 KRYS1AL-1 trial (NCT03785249) that supported the designation. Riely presented updated preliminary data during the 2021 European Lung Cancer Congress demonstrating that, when administered at a twice-daily dose of 600 mg, adagrasib induced ORRs of 43% and 45% in the phase 1/1b (n = 14) and phase 2 (n = 51) cohorts, respectively. The disease control rate was 100% in in the phase 1/1b cohort and 96% in the phase 2 cohort.

There were 2 grade 5 TRAEs, 1 case of recurrent pneumonitis, and 1 case of cardiac failure. Thirty percent of patients experienced grade 3/4 TRAEs, most often fatigue (6%), alanine aminotransferase increase (5%), and aspartate aminotransferase increase (5%).

To date, KRAS G12C inhibitors have been evaluated largely as monotherapy, but investigators have started assessing these agents in combinations (TABLE). Adagrasib is under phase 1 investigation in combination with pembrolizumab (Keytruda), cetuximab (Erbitux), and afatinib (Gilotrif) in the multiarm KRYS1AL-1 study.

Sotorasib is being examined with several agents, including trametinib (Mekinist) and the novel PD-1 inhibitor AMG 404 for KRAS G12C–mutated solid tumors, pembrolizumab and afatinib for NSCLC, and trametinib plus panitumumab (Vectibix) for advanced colorectal cancer.

GDC-6036, a novel KRAS G12C inhibitor thought to have potential antineoplastic activity, is being explored in combination with erlotinib (Tarceva) and with azetolizumab (Tecentriq) in a multiarm phase 1/2 study (NCT04449874). Investigators are also assessing the agent for patients with solid tumors in combination with bevacizumab (Avastin) and with GRC-1971, a small molecule inhibitor of SHP2; and with cetuximab for colorectal cancer.

Finally, JDQ443 is being evaluated as a treatment for patients with advanced solid tumors as monotherapy in combination with TNO155, a novel SHP2 inhibitor; and with erlotinib (Tarceva) and with atezolizumab (Tecentriq) in a multiarm phase 1/2 study (NCT04699188). When choosing drugs to pair with a KRAS G12C inhibitor, Riely recommended agents that target pathways that are important for KRAS signaling, those that affect other pathways that are important in tumor biology, and those that are otherwise a key part of NSCLC treatment.

![For a full list of references, see the article at OncLive.com.](image-url)
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Examining New Approaches to Management of Immune-Related AEs in Lung Cancer

by KRISTI ROSA

WITH THE RISE OF IMMUNOTHERAPY, patients with lung cancer are experiencing improved outcomes that have allowed for prolonged survival, but it is important to ensure that the adverse effects (AEs) associated with these novel agents are effectively managed so that their achieved efficacy does not come at the cost of quality of life (QOL).

“Corticosteroid use is related to AEs, and it’s important to keep in mind that prophylactic therapy for pneumocystis and gastritis is necessary for patients receiving more than 20 mg a day for more than 30 days. Approximately one-[fourth] of these patients will not respond, or will recur, after the use of systemic steroids,” Mario E. Lacouture, MD, said in his presentation at the 16th Annual New York Lung Cancers Symposium. “It’s important to think about the different pathways when considering alternate agents. If you are dealing with the Th1 [inflammatory pathway], you would use an IL-6 inhibitor. For Th2, you would consider an IL-4 inhibitor. If it’s mediated by B cells, you would consider rituximab [Rituxan].”

In his presentation, Lacouture, director of the oncodermatology program at Memorial Sloan Kettering (MSK) Cancer Center, an attending physician of dermatology, and a professor in the Department of Dermatology at Weill Cornell Medicine in New York, New York, outlined novel approaches to managing immune-related AEs (irAEs), how to use the skin as a tool to better understand these toxicities, and how known data can be translated to other organ systems in terms of event management.

CONSIDER THE TIMELINE AND SEVERITY OF irAEs

Timeline

When considering the timeline of irAEs, it has been observed that dermatologic toxicities are usually the first to present, appearing within 3 weeks of treatment, according to Lacouture, and these AEs are more commonly observed when PD-L1 inhibitors are combined with chemotherapy (TABLE 1).

A retrospective safety review on data from 3 trials looked at patients with advanced melanoma who received at least 1 dose of nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab at 3 mg/kg every 2 weeks. Results showed that the median time to onset of grade 3 or 4 treatment-related select AEs ranged from 3.1 weeks for skin toxicities (n = 33) to 16.3 weeks for renal toxicities (n = 7).

“Toxicities appeared up to 1 year since initiation of therapy. However, again, it is important to remember that these toxicities may appear even 2 or 3 years after patients had initiated therapy,” Lacouture said. “Another interesting observation is that when you combine cytotoxic chemotherapy with a checkpoint inhibitor, and then the cytotoxic agents are stopped, we are seeing a resurgence of toxicities perhaps because the chemotherapy is, in a way, treating some of these toxicities by blocking T- or B-cell function.”

Severity

A comprehensive review of irAEs with immune checkpoint blockade showed that when comparing several organs involved, grade 1 to 2 irAEs mainly affected the skin and the gastrointestinal tract, whereas those grade 3 to 5 were mainly restricted to the digestive tract.

“With regard to mild to moderate toxicities experienced with CTLA-4 inhibitors, skin and gastrointestinal AEs are very common, as well as with PD-1 or PD-L1 inhibitors,” Lacouture noted. “But then you see that grade 3 to 5, or severe to life-threatening to fatal, AEs are less frequent. However, pulmonary pneumonitis is the most common fatal irAE that has been reported across a meta-analysis of trials.”

Dermatologic Evaluation Sheds Light on Phenotypes

AEs are often categorized by organ type, Lacouture said, but it is important to recognize that these effects are then subject to examination by a specialist, such as a dermatologist, and then several phenotypes may appear.

In a retrospective analysis of 285 patients with 427 immune-related cutaneous AEs (irCAEs) such as pruritus (32%), maculopapular rash (28%), psoriasiform rash (5%), and others (34%), the class of checkpoint inhibitors was linked with the irCAE phenotype (P = .007), and maculopapular rash was predominant in those who received combination treatment.

“Various phenotypes…appear to also be dependent on whether a CTLA-4 inhibitor was added to a PD-1 or PD-L1 inhibitor,” Lacouture added.

Of the 120 events of maculopapular rash reported, 64 patients had received a CTLA-4 with or without a PD-1/PD-L1 inhibitor and 56 patients had just received a PD-1/PD-L1 agent. Moreover, of the 138 patients who experienced pruritus, 83 received only a PD-1/PD-L1 agent and 55 had the addition of a CTLA-4 agent. Among the 21 patients who reported bullous, 18 had just received a PD-1/PD-L1 agent and just 3 patients had the addition of a CTLA-4 agent.

In a cohort study of 73 patients with non–small cell lung cancer who received treatment with a PD-1 inhibitor, 34.2% developed autoimmune skin AEs that were more frequently experienced by those in complete or partial remission (68.2%) vs those who experienced disease progression or stable disease (19.6%), results showed.

“They collected tumor tissue, as well as tissue from the skin, and they saw that at least the T-cell infiltrates appear to be similar in both tissues at the time of the [effect]. The T-cell receptor repertoire was also analyzed and [results] showed similar clones for the T-cell receptor as it pertains to their targets in both the skin and in the
lung cancer,” Lacouture explained. “This is also recapitulated by larger meta-analyses that have demonstrated that those with lung cancer have a higher risk of pneumonitis and those with melanoma have a higher risk of skin toxicity.”

MOVING BEYOND CORTICOSTEROIDS TO MANAGE irAEs
Guidelines have been issued by American Society of Clinical Oncology, European Society for Medical Oncology, Society for Immunotherapy of Cancer, and the National Comprehensive Cancer Network to inform the appropriate use of systemic corticosteroids. However, according to Lacouture, it is important to remember that even after these agents are given, additional therapies are needed.

“We suspect that from our analysis of dermatologic events that approximately 20% of patients will not respond to corticosteroids; these are corticosteroid-refractory patients,” Lacouture said. “Also, corticosteroids are associated with their own set of AEs.” These AEs include changes in mood or sleep, body mass index increase, infection, myopathy, and dyspepsia, among others.

Patients who are refractory to corticosteroids should be considered for treatment with other biologic or targeted immunomodulating agents, according to Lacouture. “In 2% of [more than] 2700 patients with lung cancer who were treated at MSK, additional therapies were needed after corticosteroids, and this provided a resolution of AEs in approximately 50% of patients. One-[fourth] of these patients did not improve, and one-[fourth] died.”

Some of the agents that were utilized included infliximab (Remicade), vedolizumab (Entyvio), intravenous immunoglobulin, and mycophenolate mofetil, Lacouture said.5

Among the patients who had a steroid-refractory or steroid-resistant neuromuscular event (n = 5), 20% improved following the start of their second immunosuppressant, as did 30% of those with steroid-refractory or steroid-resistant pneumonitis (n = 10), 83% of those with hepatitis (n = 6), 67% of those with colitis (n = 27), and 50% of those with immune thrombocytopenic purpura (n = 2).

### TABLE. Common Timing and Severity of Immune-Related AEs in Lung Cancer

<table>
<thead>
<tr>
<th>Timing</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dermatologic toxicities are usually the first to present, appearing within 3 weeks of treatment</td>
<td>• Grade 1 to 2 effects mainly affect the skin and the gut</td>
</tr>
<tr>
<td>• AEs are more commonly observed when PD-L1 inhibitors are combined with chemotherapy</td>
<td>• Grade 3 to 5 toxicities mainly restricted to the digestive tract</td>
</tr>
<tr>
<td>• Toxicities usually appeared up to 1 year since initiation of therapy</td>
<td>• Grade 3 to 5 AEs are less frequent</td>
</tr>
<tr>
<td>• Toxicities may appear 2 to 3 years after patients have initiated therapy</td>
<td>• Pulmonary pneumonitis is the most common fatal immune-related AE</td>
</tr>
</tbody>
</table>

AE, adverse effect.

### TARGETING CUTANEOUS AEs: LOOKING CLOSER AT SPECIFIC CASES

In a patient with advanced melanoma and grade 3 bullous pemphigoid related to treatment with a PD-1 inhibitor in combination with a CTLA-4 agent who was resistant to cetirizine, diphenhydramine, mycophenolate mofetil, rituximab, prednisone, and pregabaline (Lyrica), a single subcutaneous injection of omalizumab (Xolair) at a dose of 300 mg daily resulted in partial response with reduction of the effect to grade 1 severity.6

Another patient with renal cell carcinoma and who experienced grade 3 eczematous rash and pruritus after having received treatment with nivolumab was treated with dupilumab (Dupixent), which blocks the IL-4 receptor and is a mediator of the Th2 pathway. After 4 weeks, the pruritus went from an 8 to a 2, according to Lacouture.7

David M. Faleck, MD, a gastroenterologist at MSK, has stated that endoscopic evaluation may be needed to confirm the diagnosis of immune-related colitis, as 15% to 30% of patients may receive a different diagnosis.

Moreover, Faleck has noted that the role of endoscopy is important to prognosticate. Some of these patients may have microscopic colitis, which would benefit from treatment with budesonide, whereas others may have severe colitis and require infliximab.

“Endoscopy may also help to guide therapy because steroids may be effective in only approximately 60% of cases,” Lacouture said. “As such, identifying which patients are at higher risk may allow for just taking the next step and moving to a more effective type of therapy.”

### LEVERAGING TARGETED THERAPIES TO TACKLE irAEs

A recent review paper indicated that first-line management of irAEs may largely consist of corticosteroids with or without mycophenolate mofetil, but second-line management should be based on histology of the target tissue, as well as biomarkers in the blood such as cells or antibodies, and an inhibitor that corresponds with the pathway involved, Lacouture explained.10

If the dominant mechanism of injury was determined to be lymphocytic upon immunohistopathological analysis, then potential targets would include tumor necrosis factor (TNF), IL-6, IL-17, or integrins. If determined to be mixed innate and lymphoid, then targets would include TNF, IL-6, IL-1, IL-12/IL-23, and JAK-STAT. If pauci-immune, then targets include IL-1 and JAK-STAT, whereas if eosinophilic, then the targets would be IL-5 and mTOR. If determined to be antibody mediated, the target may be CD20, and if complement mediated, then the potential targets would include C5a, IVIG, and plasmapheresis.

“The [effect] of irAEs is increasing with new approaches with combination therapies, as we have seen with the use of cytotoxic agents, and as patients are living longer, these QOL issues will become even more important,” Lacouture concluded.
Expansion Cohort Explores Efficacy of Novel Treatment for Waldenström Macroglobulinemia

by KYLE DOHERTY

TREATMENT OPTIONS FOR PATIENTS

with Waldenström macroglobulinemia (WM) are often derived from those developed for patients with multiple myeloma and other low-grade lymphomas. Patients with WM are relatively rare. Their disease is defined as lymphoplasmacytic lymphoma with involvement of the bone marrow and the immunoglobulin (Ig) M monoclonal gammopathy, novel therapeutic strategies are often difficult to develop through traditional clinical trial design.1

“[WM] is a relatively rare malignancy [and] what’s important to know is that even with current therapies—one we use traditionally including chemotherapy as well as some targeted therapies—this is a disease that's managed rather than cured,” said Radhakrishnan Ramchandren, MD, chief of the Division of Hematology/Oncology at the University of Tennessee Medical Center in Knoxville. “Another way to put that is that all patients with [WM] tend to relapse. It depends on the timing: Some patients have a longer duration of response to initial or subsequent therapies and other patients have shorter ones, and that’s based on a variety of clinical factors.”

Despite several available therapies for patients in this population, patients progress following first-line standard of care and subsequent treatment with agents such as Bruton tyrosine kinase (BTK) inhibitors that have acknowledged benefit.1 Investigators are exploring this unmet clinical need by focusing on agents that may elicit deep, durable responses with therapies that show early efficacy in patients with [WM].

EARLY EFFICACY WITH CLR 131

Phospholipid ether/phospholipid drug conjugates (PDC) may offer investigators an avenue for exploration to enhance treatment outcomes for this patient population. The novel small-molecule radiotherapeutic PDC, CLR 131, is designed to deliver cytotoxic radiation to cancer cells and stem cells.2

“[CLR 131] has a very unique mechanism [of action],” Ramchandren said. “CLR 131 uses a radioactive isotope that is attached to a compound that targets the cancer cell. What is unique about doing this is not only the use of radiation, which is not commonly used for patients with WM, but [also] that the way the mechanism targets the malignant cell is by the selective uptake and retention of phospholipid ethers, which occur more frequently and turnover occurs more frequently in cancer cells compared with normal cells.” Specifically, CLR 131 leverages its affinity to lipid rafts, allowing for internalization and delivery of the iodine 131 payload.3

The agent is under investigation in the phase 2 CLOVER-1 study (NCT02952508) in which investigators are evaluating its safety and efficacy in patients with select B-cell malignancies including multiple myeloma, indolent chronic lymphocytic leukemia, small lymphocytic leukemia, lymphoplasmacytic lymphoma, marginal zone lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, central nervous system lymphoma, and WM who have been previously treated with standard therapy.4 The study included 6 efficacy-evaluable patients with WM who had a median age of 69 years (range, 54-81), a median of 2 prior regimens (range, 1-5), and most patients (4/6) had high-risk disease; 1 patient each had intermediate-risk and low-risk disease.5 CLR 131 was administered in up to 4 intravenous infusions, each lasting approximately 15 to 20 minutes, over the course of 3 months. Patients received a mean total body dose of 92.76 mCi CLR 131.

As of the January 8, 2021, data cutoff, the overall response rate (ORR) was 100%, which included 1 complete response, 4 partial responses, and 1 major response.4 The median time to initial response was 48 days and the median duration of response (DOR) and treatment-free remission (TFR) have not been reached. Investigators reported that the mean going DOR was 335 days and the mean

FIGURE. Phase 2 Pivotal Single-Arm Study of CLR 131 for Patients With Waldenström Macroglobulinemia6,7

CLOVER-WaM (NCT02952508)

End points
Primary
• MRR
Secondary
• DOR
• TFS
• ORR

Eligibility criteria
• Histologically or cytologically confirmed WM
• ECOG performance status 0 to 2
• Life expectancy of ≥ 6 months
• Have received ≥ 2 prior lines of therapy for WM including failed or suboptimal response to a BTK inhibitor
• Measurable IgM above the upper limit of normal or ≥ 1 measurable nodal lesion with longest diameter > 15 mm or 1 measurable extranodal lesion with longest diameter > 10 mm

CLR 131
15 mCi/m² per dose for 4 doses over 2 cycles

TFS, treatment-free survival

End points
Primary
• MRR
Secondary
• DOR
• TFS
• ORR
TFR was 384 days.

“The ORR of 100% is very exciting and uncommon [for patients who have] relapsed after multiple treatments,” Ramchandren said. “What is most exciting about these data that came out regarding this agent at the [2021] American Society of Clinical Oncology Annual Meeting is that [even though] this [study] looked at a relatively small number of patients with this disease, these patients have been heavily pretreated [with] prior regimens and have largely had resistance or suboptimal responses to existing therapies,” Ramchandren said. “A very high proportion of this small population responded to the therapy despite having difficulty responding to their prior therapies or their current therapy coming into this [study].”

Common treatment-emergent adverse effects of any grade included thrombocytopenia (100%), neutropenia (83%), and anemia (66%). No cases of bleeding or febrile neutropenia were observed. All patients who experienced cytopenias recovered and the median time to resolution was 21 days.3

Ramchandren noted that these patients were also evaluated for efficacy by their molecular profiles. Patients with certain genomic alterations including MYD88 wild-type and CXCR4 wild-type disease have limited response to conventional therapies such as the BTK inhibitor ibrutinib (Imbruvica) with reported median progression-free survival (PFS) of 4.8 months in data from a phase 2 study (NCT01614821).1,5

Three of the 6 patients evaluated in CLOVER-1 had MYD88 wild-type disease and 2 of these patients were also CXCR4 wild type. The major response rate was 100% for these patients and the individual who had MYD88 wild-type disease (CXCR4 status unknown) had a complete response to treatment with CLR 131. All patients with MYD88 wild-type disease exceeded 8.5 months of follow-up and had an average TFR of 18.1 months; the median PFS was not reached.3

Investigators reported significant responses in the few patients enrolled in the trial with WM classification, leading Cellectar Biosciences, the developer of the agent, to meet with the FDA and initiate a single-arm expansion cohort of CLOVER-1 for patients with WM.2 Prior to this meeting the agent was granted fast-track designation for this patient population in May 2020 based on earlier findings from CLOVER-1.6

**CLOVER-WaM LOOKS TO EXPAND TREATMENT OPTIONS**

The phase 2 pivotal cohort was initiated by Cellectar following a Type C guidance meeting with the FDA.2 “[The CLOVER-1 data] are very intriguing and obviously very early, but it led to the desire to look at [CLR 131] in a larger number of patients and thus the expansion cohort we’re speaking of [was initiated],” Ramchandren explained.

CLOVER-WaM is a pivotal expansion cohort that will evaluate the efficacy of CLR 131 in adult patients with WM who have received at least 2 prior lines of therapy, including those who have had a suboptimal response or failed treatment with a BTK inhibitor (FIGURE 1).3 Patients will receive a total of 4 infusions of CLR 131 (15 mCi/m2) over the course of 2 cycles. Each cycle will last approximately 57 days.7

“CLR 131 is given intravenously on 4 occasions [with patients receiving] the infusion on day 1, day 15, day 57, and day 71,” Ramchandren said. “Compared with other treatments, there are [fewer] infusions and they’re more spread apart and it is of course something that we will need to watch closely as part of a clinical trial. There will be additional visits for safety and efficacy that go into [the trial design].”

CLOVER-WaM will enroll 50 patients and investigators will assess the first 10 for futility and safety. The primary end point is major response rate. Secondary end points include ORR, TFS, DOR, and clinical benefit rate.4,7

To be eligible, patients must have measurable IgM above the upper limit of normal, at least 1 measurable nodal lesion with the longest diameter greater than 15 mm, or 1 measurable extranodal lesion with the longest diameter over 10 mm.4 Patients who have undergone transplant must be 3 years out from the procedure.

Patients with a need for acute treatment of WM and those receiving anticancer therapy within 2 weeks of initial CLR 131 infusion are not eligible for the trial. Patients who have undergone prior total body or hemibody irradiation and those with prior external-beam radiotherapy resulting in greater than 20% of total bone marrow receiving greater than 20 Gy will also be excluded. Patients with secondary malignancies requiring therapy within the last 2 years or not in remission will generally be excluded, except in patients with successfully treated nonmetastatic basal cell/squamous cell skin carcinoma or prostate cancer not requiring therapy.4

Enrollment is expected to take 18 months and is under way in the United States, Europe, and Australia.2

**REFERENCES**

**Indication:** PIQRAY® (alpelisib) tablets is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer (aBC or MBC) as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

**Important Safety Information**

PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components.

**Severe Hypersensitivity:** Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of grade 3 and 4 hypersensitivity reactions was 0.7%. Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

**Severe Cutaneous Adverse Reactions (SCARs):** SCARs, including Stevens-Johnson syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY. In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of patients, respectively. DRESS was reported in patients in the postmarketing setting. If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

**PIK3CA**

Don't miss the driver of her disease—it can make her treatment clear

**The first and only therapy specifically for aBC patients with a PIK3CA mutation**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend alpelisib (PIQRAY®) + fulvestrant as a Category 1 preferred option after using a CDK4/6 inhibitor + ET
Patients with a PIK3CA mutation face a poor prognosis\(^2\)

\(~40\%\) of HR+/HER2- aBC patients have a PIK3CA mutation\(^3\)

PIQRAY + fulvestrant nearly doubled mPFS in patients with a PIK3CA driver mutation\(^4\)

PIQRAY + fulvestrant nearly doubled mPFS in patients with a PIK3CA driver mutation\(^4\)

SOLAR-1 is a double-blind, placebo-controlled, multicenter phase 3 study in men and postmenopausal women with HR+/HER2- advanced or metastatic breast cancer with or without a PIK3CA mutation whose disease had progressed or recurred on or after aromatase inhibitor-based treatment (N=572). In the PIK3CA mutation cohort (n=341), patients were randomized 1:1 to receive PIQRAY 300-mg tablets orally once daily + fulvestrant 500 mg IM\(^*\) or placebo + fulvestrant 500 mg IM.\(^*\) The primary endpoint was PFS in patients with a PIK3CA mutation by investigator assessment per RECIST v1.1.\(^{*}\)

\(^*\)Fulvestrant given on day 1 and day 15 of the first 28-day cycle, then day 1 of subsequent 28-day cycles.

SOLAR-1 is a double-blind, placebo-controlled, multicenter phase 3 study in men and postmenopausal women with HR+/HER2- advanced or metastatic breast cancer with or without a PIK3CA mutation whose disease had progressed or recurred on or after aromatase inhibitor-based treatment (N=572). In the PIK3CA mutation cohort (n=341), patients were randomized 1:1 to receive PIQRAY 300-mg tablets orally once daily + fulvestrant 500 mg IM\(^*\) or placebo + fulvestrant 500 mg IM.\(^*\) The primary endpoint was PFS in patients with a PIK3CA mutation by investigator assessment per RECIST v1.1.\(^{*}\)

Immunodeficient patients may have an increased risk of severe hypersensitivity reactions.\(^{10,11}\)

Severe cutaneous adverse reactions (SCARs) are serious and life-threatening events. If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous SCARs during PIQRAY treatment. If it is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment.

Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
Hyperglycemia: Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis has occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in the postmarketing setting.

Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG >250-500 mg/dL) and grade 4 (FPG >500 mg/dL) hyperglycemia were reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY.

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment, monitor fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. Monitor fasting glucose more frequently for the first few weeks during treatment in patients with risk factors for hyperglycemia such as obesity (BMI ≥30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥75.

If a patient experiences hyperglycemia after initiating treatment, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a health care practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes.

The safety of PIQRAY in patients with type 1 and uncontrolled type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of controlled type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified diabetic treatment. Closely monitor patients with diabetes.

Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients of the signs and symptoms of hyperglycemia (eg, excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss).

Pneumonitis: Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, can occur in patients treated with PIQRAY. Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis. Consider a diagnosis of noninfectious pneumonitis in patients presenting with nonspecific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue PIQRAY in all patients with confirmed pneumonitis. Advise patients to immediately report new or worsening respiratory symptoms.

Diarrhea: Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n=19) of patients. Based on the severity of the diarrhea, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their health care provider if diarrhea occurs while taking PIQRAY.
Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose. Refer to the full Prescribing Information of fulvestrant for pregnancy and contraception information.

The most common adverse reactions (all grades, incidence ≥20%) were diarrhea (58%), rash (52%), nausea (45%), fatigue (42%), decreased appetite (36%), stomatitis (30%), vomiting (27%), weight decreased (27%), and alopecia (20%). The most common grade 3/4 adverse reactions (incidence ≥2%) were rash (20%), diarrhea (7%), fatigue (5%), weight decreased (3.9%), nausea (2.5%), stomatitis (2.5%), and mucosal inflammation (2.1%).

The most common laboratory abnormalities (all grades, incidence ≥20%) were glucose increased (79%), creatinine increased (67%), lymphocyte count decreased (52%), gamma-glutamyl transferase (GGT) increased (52%), alanine aminotransferase (ALT) increased (44%), hemoglobin decreased (42%), lipase increased (42%), calcium decreased (27%), glucose decreased (26%), and activated partial thromboplastin time (aPTT) prolonged (21%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were glucose increased (39%), GGT increased (11%), lymphocyte count decreased (8%), lipase increased (7%), and potassium decreased (6%).

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


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PIQRAY® (alpelisib) tablets, for oral use

**INDICATIONS AND USAGE**

PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

**CONTRAINDICATIONS**

PIQRAY is contraindicated in patients with severe hypersensitivity to it or any of its components. [see Warnings and Precautions (5.1)].

**WARNINGS AND PRECAUTIONS**

**5.1 Severe Hypersensitivity**

Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, can occur in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms, including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia.

The incidence of Grade 3 and 4 hypersensitivity reactions was 0.7% [see Adverse Reactions (6)].

Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

**5.2 Severe Cutaneous Adverse Reactions**

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with PIQRAY.

In the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of the patients, respectively [see Adverse Reactions (6.1)]. Drug reaction with eosinophilia and systemic symptoms (DRESS) was reported in patients treated with PIQRAY in the postmarketing setting [see Adverse Reactions (6.2)].

If signs or symptoms of SCARs occur, interrupt PIQRAY until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

If a SCAR is confirmed, permanently discontinue PIQRAY. Do not reintroduce PIQRAY in patients who have experienced previous severe cutaneous adverse reactions during PIQRAY treatment.

If a SCAR is not confirmed, PIQRAY may require dose modifications, topical corticosteroids, or oral antihistamine treatment as described in Table 2 [see Dosage and Administration (2.3) in the full prescribing information].

Advise patients of the signs and symptoms of SCARs (e.g., a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy).

**5.3 Hyperglycemia**

Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis has occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY. Some fatal cases of ketoacidosis have occurred in patients treated with PIQRAY.

Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG > 250 to 500 mg/dL) and Grade 4 (FPG > 500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n = 2) treated with PIQRAY.

Among the patients who experienced Grade ≥ 2 (FPG 160 to 250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15 days (range, 5 to 517 days).

In the 187 patients with hyperglycemia, 87% (163/187) were managed with anti-hyperglycemic medication, and 76% (142/187) reported use of metformin as single agent or in combination with other anti-hyperglycemic medication [i.e., insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas]. In patients with Grade ≥ 2 hyperglycemia with at least 1 grade improvement (n = 153), median time to improvement from the first event was 8 days (range, 2 to 65 days).

In all patients with elevated FPG who continued fulvestrant treatment after discontinuing PIQRAY (n = 54), 96% (n = 52) of patients had FPG levels that returned to baseline.

Before initiating treatment with PIQRAY, test fasting plasma glucose (FPG), HbA1c, and optimize blood glucose. After initiating treatment with PIQRAY, monitor fasting glucose (FPG or fasting blood glucose) at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated. Monitor fasting glucose more frequently for the first few weeks during treatment with PIQRAY in patients with risk factors for hyperglycemia such as obesity (BMI ≥ 30), elevated FPG, HbA1c at the upper limit of normal or above, use of concomitant systemic corticosteroids, or age ≥ 75 [see Use in Specific Populations (8.5)].

If a patient experiences hyperglycemia after initiating treatment with PIQRAY, monitor fasting glucose as clinically indicated, and at least twice weekly until fasting glucose decreases to normal levels. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a healthcare practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes.

The safety of PIQRAY in patients with Type 1 and uncontrolled Type 2 diabetes were not established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of controlled Type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified hyperglycemic treatment. Closely monitor patients with experienced diabetes during treatment with PIQRAY.

Based on the severity of the hyperglycemia, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 3 [see Dosage and Administration (2.3) in the full prescribing information].

Advise patients of the signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often than usual or higher amount of urine than usual, or increased appetite with weight loss).

**5.4 Pneumonitis**

Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, can occur in patients treated with PIQRAY. Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, interrupt PIQRAY immediately and evaluate the patient for pneumonitis. Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms, such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Permanently discontinue PIQRAY in all patients with confirmed pneumonitis.

Advise patients to immediately report new or worsening respiratory symptoms.

**5.5 Diarrhea**

Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n = 19) of patients. Among patients with Grade 2 or 3 diarrhea (n = 71), the median time to onset was 46 days (range, 1 to 442 days).

Dose reductions of PIQRAY were required in 6% of patients and 2.8% of patients permanently discontinued PIQRAY due to diarrhea. In the 164 patients that experienced diarrhea, anti-diarrheal medications (e.g., loperamide) were required to manage symptoms in 63% (104/164) of these patients.

Based on the severity of the diarrhea, PIQRAY may require dose interruption, reduction, or discontinuation as described in Table 4 [see Dosage and Administration (2.3) in the full prescribing information].

Advise patients to start anti-diarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs while taking PIQRAY.

**5.6 Embryo-Fetal Toxicity**

Based on findings in animals and its mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes, including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures based on area under the curve (AUC) that were ≥ 0.8 times the exposure in humans at the recommended dose of 300 mg/day. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information].

Refer to the Full Prescribing Information of fulvestrant for pregnancy and contraception information.

**ADVERSE REACTIONS**

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

- Severe Hypersensitivity [see Warnings and Precautions (5.1)]
- Severe Cutaneous Adverse Reactions [see Warnings and Precautions (5.2)]
- Hyperglycemia [see Warnings and Precautions (5.3)]
- Pneumonitis [see Warnings and Precautions (5.4)]
- Diarrhea [see Warnings and Precautions (5.5)]
Table 6: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher than Placebo Arm in SOLAR-1 (All Grades)

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>PIQRAY plus fulvestrant N = 284</th>
<th>Placebo plus fulvestrant N = 287</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Dysgeusia*</td>
<td>18</td>
<td>0.4*</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>0.7*</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>52</td>
<td>20*</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0.7*</td>
</tr>
<tr>
<td>Dry skin*</td>
<td>18</td>
<td>0.4*</td>
</tr>
</tbody>
</table>
| Grading according to CTCAE Version 4.03.
1 Stomatitis: including stomatitis, aphthous ulcer and mouth ulceration.
2 Abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower.
3 Fatigue: including fatigue, asthenia.
4 Mucosal dryness: including dry mouth, mucosal dryness, vulvovaginal dryness.
5 Urinary tract infection: including UTI and single case of urosepsis.
6 Dysgeusia: including dysgeusia, ageusia, hypogeusia.
7 Rash: including rash, rash maculo-papular, rash macular, rash generalized, rash papular, rash pruritic.
8 Dry skin: including dry skin, skin fissures, xerosis, xeroderma.
* No Grade 4 adverse reactions were reported.

Among the patients with Grade 2 or 3 rash, the median time to first onset of Grade 2 or 3 rash was 12 days. A subgroup of 86 patients received prophylaxis, including antihistamines, prior to onset of rash. In these patients, rash was reported less frequently than in the overall population, for all grades rash (27% vs 54%), Grade 3 rash (12% vs 20%) and rash leading to permanent discontinuation of PIQRAY (3.5% vs 4.2%). Of the 153 patients who experienced rash, 141 had resolution of the rash.

Table 7: Laboratory Abnormalities Occurring in ≥ 10% of Patients in SOLAR-1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>PIQRAY plus fulvestrant N = 284</th>
<th>Placebo plus fulvestrant N = 287</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological parameters</td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>42</td>
<td>4.2*</td>
</tr>
<tr>
<td>Activated Partial Thromboplastin Time (aPTT) prolonged</td>
<td>21</td>
<td>0.7*</td>
</tr>
<tr>
<td>Biochemical parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased*</td>
<td>79</td>
<td>39</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>67</td>
<td>2.8*</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase (GGT) increased</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT) increased</td>
<td>44</td>
<td>3.5</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>Calcium (corrected) decreased</td>
<td>27</td>
<td>2.1</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>26</td>
<td>0.4*</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>14</td>
<td>0*</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>11</td>
<td>0.4*</td>
</tr>
</tbody>
</table>
* Glucose increase is an expected laboratory abnormality of PI3K inhibition.
* No Grade 4 laboratory abnormalities were reported.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PIQRAY. 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.

Metabolism and nutrition disorders: Hyperglycemic hyperosmolar nonketotic syndrome (HHNKS).
7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on PIQRAY

CYP3A4 Inducer

Co-administration of PIQRAY with a strong CYP3A4 inducer may decrease alpelisib concentration [see Clinical Pharmacology (12.3) in the full prescribing information], which may decrease alpelisib activity. Avoid co-administration of PIQRAY with strong CYP3A4 inducers.

Breast Cancer Resistance Protein Inhibitors

Co-administration of PIQRAY with a breast cancer resistance protein (BCRP) inhibitor may increase alpelisib concentration [see Clinical Pharmacology (12.3) in the full prescribing information], which may increase the risk of toxicities. Avoid the use of BCRP inhibitors in patients treated with PIQRAY. If unable to use alternative drugs, when PIQRAY is used in combination with BCRP inhibitors, closely monitor for increased adverse reactions.

7.2 Effect of PIQRAY on Other Drugs

CYP2C9 Substrates

Co-administration of PIQRAY with CYP2C9 substrates (e.g., warfarin) may reduce plasma concentration of these drugs [see Clinical Pharmacology (12.3) in the full prescribing information]. Closely monitor when PIQRAY is used in combination with CYP2C9 substrates where decreases in the plasma concentration of CYP2C9 substrates may reduce activity of these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

PIQRAY is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for pregnancy information.

Based on animal data and mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes, including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures ≥ 0.8 times the exposure in humans based on AUC at the recommended dose of 300 mg/day (see Data). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

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

Data

Animal Data

In embryofetal development studies in rats and rabbits, pregnant animals received oral doses of alpelisib up to 30 mg/kg/day during the period of organogenesis. In rats, oral administration of alpelisib resulted in maternal toxicity (body weight loss, low food consumption) and no viable fetuses (post-implantation loss) at 30 mg/kg/day (approximately 3 times the exposure in humans at the recommended dose of 300 mg/day based on AUC). At a dose of 10 mg/kg/day (approximately 0.8 times the exposure in humans at the recommended dose of 300 mg/day based on AUC), toxicities included reduced fetal weight and increased incidences of skeletal malformations (bent scapula and thickened or bent long bones) and fetal variations (enlarged brain ventricle, decreased bone ossification).

In a pilot embryofetal development study in rabbits, a dose of 30 mg/kg/day resulted in no viable fetuses (post-implantation loss). Doses ≥ 15 mg/kg/day resulted in increased embryo-fetal deaths, reduced fetal weights, and malformations, mostly related to the tail and head. At 15 mg/kg/day in rabbits, the maternal exposure was approximately 5 times the exposure achieved at the recommended human dose of 300 mg/day based on AUC.

8.2 Lactation

PIQRAY is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for lactation information.

There is no data on the presence of alpelisib in human milk, its effects on milk production, or the breastfed child. Because of the potential for serious adverse reactions in the breastfed child, advise lactating women not to breastfeed during treatment with PIQRAY and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

PIQRAY is used in combination with fulvestrant. Refer to the Full Prescribing Information of fulvestrant for contraception and infertility information.

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating PIQRAY.
Practice-Changing and Reaffirming Data Set Up an Exciting Future in Melanoma

by COURTNEY MARABELLA

POSITIVE DATA READOUTS FROM studies, such as the phase 2/3 RELATIVITY-047 trial (NCT03470922) with relatlimab and nivolumab (Opdivo) and the phase 3 KEYNOTE-716 trial (NCT03553836) with pembrolizumab (Keytruda), cemented 2021 as a banner year for the treatment of patients with melanoma, across various stages and subtypes, according to Meredith McKean, MD, MPH.

Specifically, data from RELATIVITY-047 concerned patients with untreated metastatic or unresectable melanoma who received a fixed-dose combination of the LAG3-blocking antibody relatlimab plus nivolumab or nivolumab alone. The data were stratified by mutational profiles including LAG3 expression on immune cells, PD-L1 expression on tumor cells, and BRAF status.1 The KEYNOTE-716 data highlighted the use of pembrolizumab as adjuvant treatment for patients with resected high-risk stage II melanoma vs placebo.

At the European Society for Medical Oncology Congress 2021, investigators presented updated efficacy findings from RELATIVITY-047, which showed that patients who received a fixed-dose combination of relatlimab and nivolumab (n = 355) had superior progression-free survival (PFS) and a tolerable safety profile compared with those who received nivolumab alone (n = 359).

Specifically, the median PFS was 10.12 months (95% CI, 6.37-15.74) vs 4.63 months (95% CI, 3.38-5.62), respectively (HR, 0.75; 95% CI, 0.62-0.92; P = .0055). Based on these data, the FDA granted a priority review to the biologics license application for the combination as treatment for adult and pediatric patients 12 years and older weighing at least 40 kg and who have unresectable or metastatic melanoma.2

Recurrence-free survival (RFS) data from KEYNOTE-716 supported the use of adjuvant pembrolizumab for patients with earlier-stage disease who have a high risk of recurrence similar to that among those with stage IIIA and IIIB melanoma. The median RFS was not reached (NR) in either arm of the trial: pembrolizumab (n = 487; 95% CI, 22.6-NR) vs placebo (n = 489; 95% CI, NR-NR). In the pembrolizumab arm, 11.1% of patients experienced RFS events compared with 16.8% among those in the placebo arm (HR, 0.73; 95% CI, 0.58-0.94; P = .00658).

In an interview with OncologyLive®, McKean, the associate director of the Melanoma and Skin Cancer Research Program at Sarah Cannon Research Institute at Tennessee in Nashville, discussed the most pivotal data for the treatment of patients with melanoma that read out in 2021 (TABLE 1,3,4), and what is on the horizon for the space in 2022.

TABLE. Efficacy Outcomes in Melanoma Trials1,3,4

<table>
<thead>
<tr>
<th>Trial</th>
<th>Outcome</th>
<th>Relatlimab and nivolumab (n = 355)</th>
<th>Nivolumab (n = 359)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELATIVITY-047 (NCT03470922)</td>
<td>Median PFS, months (95% CI)</td>
<td>10.12 (6.37-15.74)</td>
<td>4.63 (3.38-5.62)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.75; 95% CI, 0.62-0.92; P = .0055</td>
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</tr>
<tr>
<td></td>
<td>12-month PFS rate (95% CI)</td>
<td>47.7% (41.8%-53.2%)</td>
<td>36.0% (30.5%-41.6%)</td>
</tr>
<tr>
<td>KEYNOTE-716 (NCT03553836)</td>
<td>Median RFS, months (95% CI)</td>
<td>NR (22.6-NR)</td>
<td>NR (NR-NR)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.65; 95% CI, 0.46-0.92; P = .00658</td>
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</tr>
<tr>
<td></td>
<td>12-month RFS rate</td>
<td>90.5%</td>
<td>83.1%</td>
</tr>
<tr>
<td>IMCgp100-202 (NCT03070392)</td>
<td>Median OS, months (95% CI)</td>
<td>21.7 (18.6-28.6)</td>
<td>16.0 (9.7-18.4)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.51; 95% CI, 0.37-0.71; P &lt; .001</td>
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<tr>
<td></td>
<td>12-month OS rate (95% CI)</td>
<td>73% (66%-79%)</td>
<td>59% (48%-67%)</td>
</tr>
<tr>
<td></td>
<td>6-month PFS rate</td>
<td>3.3 (3.0-5.0)</td>
<td>2.9 (2.8-3.0)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.73; 95% CI, 0.58-0.94; P = .01</td>
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<td>HR, 0.73; 95% CI, 0.58-0.94; P = .01</td>
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</tr>
</tbody>
</table>

NR, not reached; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.

*Investigator’s choice included single-agent pembrolizumab, ipilimumab, or dacarbazine.

Q What have been the most notable or practice-changing studies in melanoma in 2021?

2021 has been a big year for melanoma, and that has been exciting. [In the years leading up to 2021,] we could see more progress was being made in some of the immunotherapy studies, so it has been exciting to see some breakthroughs.

The biggest headline [of 2021] is the RELATIVITY-047 trial. This [study examined] relatlimab, which is an anti-LAG3 monoclonal antibody, plus nivolumab as a first-line therapy for patients with previously untreated metastatic melanoma. [The] combination [was examined] vs
single-agent nivolumab. [The study has] been presented at 2 conferences at this point, [and results have demonstrated] a more than doubling of the PFS benefit vs single-agent nivolumab, which is exciting. The data [have shown that the combination has] been well tolerated, and this could be a great option for patients in the future.

There are still several questions remaining, and we are waiting to see more data on response rates and overall survival [OS]. Ipilimumab [Yervoy] plus nivolumab is still the bar for the frontline treatment of melanoma, so where this combination fits in the paradigm is still a big question.

Another study that was exciting to see was the KEYNOTE-716 trial. This was a phase 3 study of pembrolizumab for patients with stage IIIIB and stage IIC melanoma. We have known that this is a patient population with a high risk of recurrence, so it was exciting to see the results demonstrating a 12-month RFS benefit in this group. This is still going to require a conversation with each patient, recognizing that we are still seeing the same toxicity we have seen in other immunotherapy studies. Grade 3/4 toxicities [were reported in] approximately 16% of patients in the study, so discussing the RFS benefit vs some of the toxicities [with patients will be important]. However, it is going to be great to have this option moving forward.

[Finally, the other] top study was the phase 2 [IMCgp100-202] trial [NCT03070392], in which investigators examined tebentafusp [IMCgp100] in patients with uveal melanoma. It has been tough to try to find effective therapies [in the uveal melanoma space], and this is the first treatment that has finally shown an OS benefit for this population. [However,] there are some caveats. The response rate was 9%, which may just indicate how difficult it is to assess response in these patients who tend to have a significant amount of disease in the liver. Also, this is still only going to be an option for approximately 50% of patients with metastatic uveal melanoma.

Tebentafusp is a bispecific fusion protein targeting gp100 on tumor cells, and an anti-CD3 T cell–engaging domain, so it does require patients to have HLA-A*02:01-positi
tive disease. For the patients [who] do not have that, this still will not be an option, but to finally see some progress in uveal melanoma has been exciting (TABLE 1).<ref>

Please discuss long-term follow-up data from previous studies that we saw presented this year.

There was quite a bit of long-term [follow-up] data presented throughout the year. We saw the 6.5-year benefit of ipilimumab plus nivolumab [from the phase 3 CheckMate 067 trial (NCT01844505)]. It was exciting to see that at 6.5 years out, approximately 50% of patients are still alive. That was a huge landmark for patients with melanoma, their family members, and [investigators] to see how far we have come, but also to see how far we still have to go.

There were also several long-term follow-ups for some of the stage 3 adjuvant studies, such as the phase 3 KEYNOTE-054 trial [NCT02362594] with pembrolizumab and the phase 3 CheckMate 915 trial [NCT03068455] with nivolumab. [These trials] affirmed that we continue to see a RFS benefit in the population [with stage III disease], which has been nice. Furthermore, we are continuing to see more data on how to manage [patients with stage IV, resected disease and brain metastases]. We saw the phase 2 IMMUNED trial [NCT02523313] demonstrating the benefit [of treatment with] ipilimumab and nivolumab. There were a lot of studies this year that reaffirmed some of the practices that we had started implementing from that early data.

Is there any research that you are currently involved in and would like to highlight?

There is a lot of exciting research ongoing for cutaneous melanoma, as well as great interest in some of the more challenging subtypes. We are seeing excitement for some of the [messenger RNA] vaccines, some novel immunotherapy combinations, and [efforts] trying to target molecular drivers that previously had not been targets, such as patients with NRAS mutations, for example. [Additionally,] reaching out into these rarer subtypes, [such as] uveal melanoma, after having some early success with tebentafusp, and seeing several other targeted therapy trials and specific treatment options just for those patients, has been exciting to be a part of.

As we head into 2022, what is on the horizon for melanoma?

There are a couple of exciting areas. In the metastatic setting, we are waiting on additional results and follow-up from the phase 3 [PIVOT IO 001] study [NCT03635983] examining NKTR-214 [(bempegaldesleukin) plus nivolumab] in the frontline setting. That is going to be an exciting study to watch.

In a different space, the work being done in neoadjuvant melanoma has been exciting to see. That is a fascinating space because we have seen, in other tumor types, that [neoadjuvant therapy] is beneficial for patients. The learning that is involved in being able to understand how these compounds work, which patients are benefitting, and the strides being made there has been exciting to follow. We are learning so much about which combinations look to be beneficial, and that, oftentimes, radiographic responses are underestimating pathologic responses. We are also learning a lot about tolerability and the immune response in that very early setting, so we are going to continue to see more and more in that space.

REFERENCES


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

Targeted Therapies Make Major Strides in mCRC Treatment

by CAROLINE SEYMOUR

THE TREATMENT ALGORITHM IN metastatic colorectal cancer (mCRC) has gone from accounting only for the sidedness of the primary tumor, performance status, volume of disease, and potential resectability to also include the genetics of the tumor, particularly for patients in need of second-line therapy, explained Christine M. Parseghian, MD. “For several years, we were stuck with regorafenib [Stivarga] and TAS-102 [trifluridine/tipiracil; (Lonsurf)], and thankfully just over the past few years we’ve seen immunotherapy come in, HER2-directed therapy make its way from breast and gastric cancer over to CRC, as well as [patients with] BRAF-mutated disease [becoming] eligible for BRAF inhibitors and seeing incredible responses with NTRK inhibitors in patients with NTRK fusions,” said Parseghian at the 39th Annual Chemotherapy Foundation Symposium (CFS®): Innovation Cancer Therapy for Tomorrow®, a program hosted by the Physicians’ Education Resource® (PER®), LLC.1

BRAF V600E MUTATIONS

BRAF V600E mutations are present in upward of 10% of patients with CRC and are associated with a median overall survival (OS) of 11 months vs 30 months in those without the mutation, said Parseghian, an assistant professor in the Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston. However, the results of the phase 3 BEACON CRC trial (NCT02928224) showed that patients with BRAF V600E mutations who received the combination of encorafenib (Brafvo) and cetuximab (Erbitux)—which is approved by the FDA—with or without binimetinib (Mektovi) as second-line or third-line therapy had a median OS of 9.3 months vs 5.9 months with standard chemotherapy.2

“Given the nice responses in the second-line and third-line settings, we are now trying to see how we can improve outcomes in patients who we know are BRAF mutated from the get-go,” Parseghian said. To that end, the phase 2 ANCHOR-CRC trial (NCT03693170) is evaluating the combination of encorafenib and cetuximab with binimetinib as frontline therapy in patients with mCRC.

PRELIMINARY FINDINGS FROM THE STUDY, which were presented at the 2021 Gastrointestinal Cancers Symposium, demonstrated that the triplet regimen elicited an objective response rate (ORR) of 47.8% (n = 44), with a “remarkable” disease control rate (DCR) of 88%, Parseghian explained.3

HER2 OVEREXPRESSION

HER2 overexpression is more commonly found in left-sided tumors vs right-sided tumors, with a 5% prevalence rate in RAS wild-type tumors vs 2.5% in RAS-mutant tumors, said Parseghian. Several anti-HER2 combinations have been studied in patients with chemotherapy-refractory HER2-positive mCRC, such as in the phase 2 HERACLES (NCT03225937) and My Pathway (NCT02091141) trials. In HERACLES, patients who received the combination of trastuzumab (Herceptin) and lapatinib (Tykerb) experienced a “really nice” ORR of 30% and a median duration of response (DOR) of 8.7 months, Parseghian said.4 Notably, investigators defined HER2 positivity as immunohistochemistry (IHC) of 3+ or IHC of 2+ and fluorescence in situ hybridization positivity.

“The regimen was very well tolerated in the refractory setting, with some gastrointestinal toxicities and hypokalemia,” Parseghian said. In My Pathway, patients who received the combination of trastuzumab and pertuzumab (Perjeta) experienced an ORR of 32% and a median DOR of 6.1 months, showing similar activity and tolerability as trastuzumab/lapatinib, said Parseghian.5

Parseghian also called attention to the phase 2 MOUNTAINEER (NCT03043313) and DESTINY-CRC01 (NCT03384940) trials. In MOUNTAINEER, patients with chemotherapy-refractory and VEGF-refractory and RAS wild-type who received the combination of trastuzumab and tucatinib (Tukysa) derived an ORR of 55%. In the overall population, the median progression-free survival (PFS) of 6.2 months.6 “We’re seeing really incredible responses with this combination considering a lot of these patients had more than 2 prior lines of therapy,” Parseghian said.

In DESTINY-CRC01, patients who had received at least 2 prior regimens experienced an ORR of 45% with the antibody-drug conjugate (ADC) fam-trastuzumab deruxtecan-nxki (Enheru).7 One caveat of the study that distinguishes it from prior trials with HER2-directed therapies is that patients could have received prior HER2-directed therapy, Parseghian said.

“This combination is really a nice option even for patients who have progressed on dual HER2-directed therapy,” Parseghian said. “Dual HER2-directed therapy and ADCs have robust activity in HER2-positive mCRC with a favorable toxicity profile and exceed outcomes as expected from second-line options, which is very exciting.”

MSI-H

Although pembrolizumab (Keytruda) has been approved since 2017 for patients with pretreated microsatellite instability-high (MSI-H) mCRC, it was not until recently that data were reported to support its move into the frontline setting, explained Parseghian, citing results of the phase 3 KEYNOTE-177 trial (NCT02563002). In the study, patients with MSI-H mCRC experienced improved PFS (HR, 0.59) when treated with frontline pembrolizumab vs investigator’s choice chemotherapy.4 The median PFS was 15.5 months vs 8.2 months, respectively. Although the median OS was not reached vs 36.7 months (HR, 0.74), respectively, OS benefit was not proven. Notably, 60% of patients crossed over to the pembrolizumab arm, which may have confounded the results, Parseghian said.

Other checkpoint inhibitors that have been studied in the pretreated setting include nivolumab (Opdivo) alone and in combination with ipilimumab (Yervoy) in the phase 2 CheckMate 142 trial (NCT02060188). In the
study, nivolumab led to an ORR of 31%, a 69% DCR at 12 weeks, and a 1-year PFS rate of 50%. With the combination, an ORR of 55% was reported, with an 80% DCR, and a 1-year PFS rate of 71%,16

“This dual checkpoint approach is really a nice option for patients with good performance status,” Parseghian said. “We do see some increase in the immunogenic adverse effects, but really not significant enough to withhold this as an option.”

Another checkpoint inhibitor now approved for use is dostarlimab-gxly (Jemperli), which received an accelerated approval for patients with mismatch repair–deficient recurrent or advanced solid tumors, as determined by an FDA-approved test, who have progressed on or following previous treatment and who have no satisfactory alternative options.11 The approval was based on findings from the multicohort phase 1 GARNET trial (NCT02715284), in which the PD-1 inhibitor led to an ORR of 36.2% in patients with CRC.12

**NTRK FUSIONS**

Fusions, although enriched in MSI-H tumors, are rare, occurring in less than 1% of patients with mCRC. However, patients with gene fusions can experience deep and durable response when paired with the appropriate targeted therapy, explained Parseghian. In the case of NTRK, both larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) are approved for use, having shown ORRs of 50% and 25%, respectively, in patients with CRC.13,14 “We’re seeing really wonderful data [with these agents], which represent nice options [for patients],” said Parseghian.

**KRAS G12C MUTATIONS**

Finally, Parseghian highlighted the most recent druggable target of interest, KRAS G12C, for which there are now 2 agents under investigation in mCRC: sotorasib (Lumakras) and adagrasib. “We’ve been trying to [effectively] target KRAS for decades, so this is really the first time that we’ve been able to do something [for these patients],” Parseghian said.

Both agents have been studied alone and in combination with EGFR inhibitors. In the case of sotorasib, the agent induced an ORR of 7.1% and a median DCR of 73.8% in the phase 1 CodeBreaK 101 trial (NCT04185883)15; when paired with panitumumab (Vectibix), the ORR and DCR were 26.9% and 80.8%, respectively.16 In the phase 1/2 KRYS TAL-1 study (NCT03785249), adagrasib monotherapy led to an ORR of 22% and a median DCR of 87%; in combination with cetuximab (Erbitux), the ORR and DCR were 43% and 100%, respectively.17

“[Sotorasib and adagrasib] are oral drugs, especially when they’re given as monotherapy, and they’re extremely well tolerated in patients who would otherwise be getting very toxic third-line agents,” Parseghian said. “We wouldn’t have been able to make these advances had it not been for these very recent trials, so it’s really important that we encourage all our patients to join these big clinical trials as new and exciting therapies come their way.”

**REFERENCES**

advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

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

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

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

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

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS\(^{1,2}\)

**OVERALL POPULATION**
(N=733)

\[ \begin{align*}
38\% & \text{ Reduction in the risk of progression or death} \\
\text{MEDIAN PFS: 13.8 MONTHS WITH ZEJULA} & \text{ VS 8.2 MONTHS WITH PLACEBO} \\
(\text{HR, 0.62; 95\% CI, 0.50-0.76}) & \text{ P<0.0001}
\end{align*} \]

**HRd POPULATION**
(n=373)

\[ \begin{align*}
57\% & \text{ Reduction in the risk of progression or death} \\
\text{MEDIAN PFS: 21.9 MONTHS WITH ZEJULA} & \text{ VS 10.4 MONTHS WITH PLACEBO} \\
(\text{HR, 0.43; 95\% CI, 0.31-0.59}) & \text{ P<0.0001}
\end{align*} \]

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

**Important Safety Information (continued)**

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

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

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

**Please see Brief Summary on the following pages.**

**References:**

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

Visit [ZEJULAHCP.COM](http://ZEJULAHCP.COM) to explore the PRIMA data.

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Produced in USA.
5.3 Hypertension and Cardiac Events

Hypertension and hypotensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

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

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

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

5.4 Posterior Reversible Encephalopathy Syndrome

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

Monitor all patients treated with ZEJULA for signs and symptoms of PRES. If PRES is suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reintroducing ZEJULA in patients previously experiencing PRES is not known.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) of full prescribing information). ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicity studies were not conducted with niraparib.

Aprosir pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA (see Use in Specific Populations (8.1, 8.3)).

5.6 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

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

6. ADVERSE REACTIONS

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

- MDS/AML (see Warnings and Precautions (5.1))
- Bone marrow suppression (see Warnings and Precautions (5.2))
- Hypertension and cardiovascular effects (see Warnings and Precautions (5.3))
- Posterior reversible encephalopathy syndrome (see Warnings and Precautions (5.4))

6.1 Clinical Trials Experience

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

The most common adverse reactions of all grades in >10% of 1,314 patients who received ZEJULA in the pooled PRIMA, NOVA, and QUADRRA trials were nausea (65%), thrombocytopenia (65%), anemia (58%), fatigue (52%), constipation (39%), mucositis (31%), decreased appetite (24%), leucopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (10%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomania (11%).
Patients receiving ZEJULA with dose based on baseline weight or platelet count. Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anaemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anaemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anaemia (23%), and neutropenia (15%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=454)</th>
<th>Placebo (n=224)</th>
<th>ZEJULA (n=464)</th>
<th>Placebo (n=224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>54</td>
<td>36</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Nausea</td>
<td>54</td>
<td>36</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
<td>36</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
<td>15</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>9</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>8</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>8</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>8</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anaemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days. Table 5 and Table 6 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZEJULA in NOVA.

*Common Terminology Criteria for Adverse Events version 4.0.
*Includes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.
6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders: Pancytopenia.

Immune System Disorders: Hypersensitivity (including anaphylaxis).

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES).

Psychiatric Disorders: Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).

Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

Skins and Subcutaneous Tissue Disorders: Photosensitivy.

Vascular Disorders: Hypertensive crisis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women (see Clinical Pharmacology (12.1) of full prescribing information).

There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risks. ZEJULA may have the potential to cause teratogenicity and/or embryo-fetal death when administered to pregnant women. Therefore, ZEJULA is contraindicated in pregnant women. ZEJULA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.3)).

The use of ZEJULA in pregnant women to inform the drug-associated risk.

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

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

8.3 Females and Males of Reproductive Potential

ZEJULA can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.3)).

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

Contraception

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In PRIMA, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. In NOVA, 35% of patients were aged 65 years or older and 8% were aged 75 years or older. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater severity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mild (Clcr: 60 to 89 mL/min) to moderate (Clcr: 30 to 59 mL/min) renal impairment.

The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

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

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

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

17 PATIENT COUNSELING INFORMATION

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

8.8 Adverse Reactions

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

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83/10</td>
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<td>66/6</td>
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<td>40/8</td>
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</tr>
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AST/ALT = Aspartate transaminase/alanine aminotransferase.

Common Terminology Criteria for Adverse Events version 4.02.

Includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normochromic normocytic anemia.

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

Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection, and neutropenic sepsis.

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

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6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders: Pancytopenia.

Immune System Disorders: Hypersensitivity (including anaphylaxis).

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES).

Psychiatric Disorders: Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).

Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

Skins and Subcutaneous Tissue Disorders: Photosensitivity.

Vascular Disorders: Hypertensive crisis.

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With No Replacement for OCM on the Horizon, Oncology Practices Ask: What Now?

by GIANNA MELILLO

IF ONCOLOGY PRACTICES EXPECTED

an explanation from the CMS on next steps following the imminent end of the Oncology Care Model (OCM) during CMS Innovation Center’s (CMMI’s) announcement of a “strategic refresh” earlier this year, they may have been disappointed.1

The OCM, which began in 2016, has an anticipated performance period end date of June 2022.2 For many participating practices, what follows is up in the air. “I think a lot of us had the expectation there would be a gap, and I think the lack of hearing anything otherwise just makes it more [clear] that there will be a gap,” said Stephen M. Schleicher, MD, MBA, a medical oncologist at Tennessee Oncology and medical director of value-based care at OneOncology in Nashville. “I’m afraid that priority on a next-generation cancer model may be even more delayed than some of us had hoped.”

As part of its strategic refresh announcement, Elizabeth Fowler, PhD, JD, deputy administrator and director of CMMI, said the center did not plan to end any models early, although objectives of the refresh will guide revisions to existing models and consideration of future models. The new approach will also focus on a “streamlined portfolio of models,” as the previous volume led to confusion among participating practices. “In addition to reducing overlap, we also want our models to be simpler and easier to participate in, with less administrative burden,” Fowler said.

CMS declined to comment directly for this article. A spokesperson said there is likely to be some gap between the end of OCM and the start of any potential oncology model.

UNCERTAINTY GROWS

This raises a myriad of challenges and questions for those enrolled in OCM who have complied with data reporting and operational requirements for the past 5 years. When it launched, OCM was to expire in 2021, but because of the pandemic, a proposed successor model called Oncology Care First was shelved.

“It actually feels more like a void than merely a potential gap in the comprehensive care that a lot of patients are now receiving and benefiting from under this model,” said Karen L. van Caulil, PhD, president and chief executive officer of the Florida Alliance for Healthcare Value in Winter Springs. Intended to increase value-based care in the oncology field, OCM provides participants with monthly enhanced oncology services (MEOS) payments in addition to regular fee-for-service Medicare payments. Whether practices will receive bridge payments to continue funding services such as navigators and 24/7 record access until a new model is implemented remains to be seen.

“What do you do when you don’t have those payments anymore?” Schleicher asked. “We’re lucky Tennessee Oncology is very large, and we will continue to provide high-quality care that we’ve learned to do through OCM. But if you’re a small practice, I worry, are practices going to have to revert back to the old ways of doing things where they don’t have support from Medicare along the way?”

Amid this uncertainty, the Community Oncology Alliance (COA) called on CMMI to extend OCM through December 31, 2022.3 In a letter sent November 16, the group cited the investment that practices have made in the model, along with the effect the model has had on patient care. COA also argued that some negative reviews of OCM, notably the Abt Associates’ evaluation, failed to capture later data that show practices became better at implementing the model over time.4

“The millions of dollars of taxpayers’ money invested in the OCM and the dramatic successes of many independent community oncology practices participating in the OCM in enhancing patient cancer care while lowering treatment costs should be clear reasons why the OCM should not be trashed, but refined and reenvisioned based on what is working,” the letter stated. COA strongly endorsed CMMI’s call to focus on health equity in a future model.

This move received support from the Florida Alliance for Healthcare Value. “We think that’s a very reasonable and appropriate request [by COA], rather than to just completely stop the program entirely,” van Caulil said.

Higher quality, more coordinated care at the same or lower cost than Medicare, was the primary target of OCM; the voluntary model also allowed practices to opt into 1- or 2-sided risk.

Absence of OCM raises regulatory compliance issues as well. Once the model ends, the possibility is raised that by default,
OCM practices would be governed by other elements of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Under MACRA, if practices were enrolled in an alternative payment model (APM), they did not have to abide by the Merit-Based Incentive Payment System (MIPS). But if OCM expires and practices find themselves no longer enrolled in an APM, it is unclear if that fact compels MIPS participation.

CHALLENGES IN OCM

Despite mixed reports of success with the model, various shortcomings hindered efficient implementation and participation for some practices and ought to be addressed in future iterations, experts argued.

Because of OCM’s structure, participation in the model could disincentivize providing care for underserved communities or high-risk patients. Despite meeting reporting requirements and following guidelines, practices serving populations with baseline poor health would necessarily have increased risks of worse overall outcomes compared with practices serving healthier populations. In a paper presented at the 2021 American Society of Clinical Oncology Annual Meeting investigators found, for example, that high-risk patients were, on average, $21,500 over target when undergoing autologous stem cell transplant, even with risk adjustment for this procedure.6

“Provider exposure to risk in the OCM is highly sensitive to factors at the cancer and patient level,” wrote the authors, who called for models that “model risk in more clinically granular ways.”6

In their strategic refresh, CMMI acknowledged this problem, which was also apparent in earlier additional models.

“My vision for the future of the agency, our programs, and the people we serve is straightforward: that CMS serve the public as a trusted partner and steward, dedicated to advancing health equity, expanding coverage, and improving health outcomes,” said CMS Administrator Chiquita Brooks-LaSure during the refresh announcement.

Among lessons learned listed in an accompanying CMMI whitepaper, the center stressed that moving forward, health equity will be embedded into every model. This step was seen by many as encouraging.7

“So far, models have focused on cost, quality, and patient experience. [Adding] equity as one of the factors is a welcome change,” said Kashyap Patel, MD, CEO of the Carolina Blood and Cancer Care Associates, associate editor of Evidence-Based Oncology™, and president of COA.

But rising treatment costs in the oncology space also posed a challenge to practices. OCM includes a reimbursement system based on a snapshot of time to calculate reimbursement rates for oncology treatments. Over the years as new, more expensive treatments were developed and approved, they were, at times, not accurately captured by the model. The model was so ill-equipped to handle major innovations that CMMI initially did not even include chimeric antigen receptor T-cell therapy in the cost-of-care calculations.6

Cancer is a multifaceted disease with numerous variations, types, and mutations. This heterogeneity complicates standardization of care—a key component of other, more streamlined payment models.

CMMI plans to begin the Radiation Oncology (RO) Model in January 2022,8 a start date the American Society for Radiation Oncology has deemed “extremely challenging,” in part because of recently permitted cuts in Medicare fee schedules.9

The RO model “tests whether prospective, site-neutral, modality-agnostic, episode-based payments to physician group practices, hospital outpatient departments, and freestanding radiation therapy centers for radiotherapy episodes of care [reduce] Medicare expenditures while preserving or enhancing the quality of care for Medicare beneficiaries.”10

Under this model, there are limited options for treatment, and its mandatory nature encourages uniformity across practices. However, compulsory participation brings along its own challenges.

It is unclear if OCM’s successor will be mandatory. Although this change would remove selection bias when it comes to covering certain patient populations, a mandatory model would also impose onerous data-reporting requirements on smaller practices with less resources and manpower, adding to compliance hurdles.

On the flipside, voluntary models allow practices to simply drop out at the first hint of a bleak financial forecast, limiting the quality and quantity of data produced by model participation.

During OCM’s 5-year implementation, changing conditions required by CMS and a lag in outcome reports meant practices were unable to implement successful practices in a timely fashion.

LOOKING AHEAD

Moving forward, CMMI plans to increase stakeholder perspectives and feedback on model successes and challenges via listening sessions hosted throughout the year—the first of which took place on November 18.

During this session, Lalan Wilfong, MD, vice president of care relations and practice transformation at McKesson and a medical oncologist and hematologist at Texas Oncology, laid out some complications of OCM and subsequent RO model participation.

Wilfong discussed how these practices will have to submit data for the mandatory RO model through a different platform than that used for OCM. This inconsistency presents a hurdle for practices as it took some years to optimize data reporting procedures to minimize compliance burdens.

With a new data reporting format under the RO model, “it feels like we have to start over again,” Wilfong said. But improved alignment from CMMI in the future may help alleviate these challenges and enable model participation, he added.

Touching on the heterogeneity of cancer care, Wilfong explained how historical benchmarks may not accurately reflect the current care provided. For example, at the start of the OCM, lung cancer care was “very simple in the management at that time,” but over the past few years, has seen “tremendous innovation.”

“My care paths for patients with lung cancer are very complex now, where they used to be pretty simple, with very different costs and outcomes and toxicities that we manage,” Wilfong said. Putting appropriate benchmarks in place for oncology patients that reflect the changing nature of the treatment landscape will help encourage rural and smaller practices to participate in future models.

Although this session was broad in scope, in upcoming discussions stakeholders may be eager to know whether practices that invested in models and reported success will be recognized in future or replacement models.
OncLive® is launching a new app called Meet My MSL!

Meet My MSL has been created to provide oncologists the opportunity to initiate direct contact with the Medical Science Liaison (MSL) in their area of expertise. It has never been easier to meet, locate, and contact the MSL you need.

Meet My MSL precisely facilitates introductions and connections between physicians, MSLs, and other essential professionals. Only those who meet your search criteria will be displayed.

Key Benefits and Features

- No more guesswork about whom to connect with for information
- User-friendly search and quick links to facilitate an introduction to local MSLs
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- Medical professionals can enhance the search and filter results until they find the MSL they would like to contact
- Each MSL will have a profile page for you to access before contacting

Find any MSL from any company for any tumor
OCM, CONTINUED FROM PAGE 82

“If you want to continue to garner enthusiasm for participating in APMs and get people excited about it, there needs to be some recognition of groups that did double down on OCM—the first of its type—and especially the ones that are taking 2-sided risk,” Schleicher said. “It is frustrating for us in that boat who made all these large practice-transformation efforts, and hired new teams, and invested in analytics, and have been messaging to everybody around us how important this is to then feel like the rug got ripped from below us.”

Before practices invest in infrastructure and change how they operate in preparation for the next model, the concern is they participate for a few years, the model ends, and what comes next is unknown, he explained.

Overall, Schleicher does not think OCM was a failure and hopes it doesn’t get remembered as such, stressing the model resulted in improved care and cost savings for Tennessee Oncology.

Using MEOS payments, the practice was able to better reach rural patients and help them navigate a complex care journey by creating a new health care infrastructure that incorporates care coordination and data analytics. Performing well in OCM also enabled the practice to take on major goals of accountable care organizations, including keeping patients out of hospitals and improving end-of-life care.

At the time of publication, Tennessee Oncology received word that for the period spanning the second half of 2019 and the first half of 2020, the community practice received a 100% quality score under the model, for metrics that include patient pain, depression assessment and management, reduction in emergency department visits, and appropriate use of hospice. Tennessee Oncology also saved Medicare $5 million during this period.1

Schleicher aims to continue these efforts even after OCM ends. “It’s the right thing to do for patients....I think OCM was a success for groups like us,” he said. “We learned how to provide better care, and we couldn’t have done that without this model.”

Hayden E. Klein contributed to this report.

Third-Party Financing Offers a Path Forward for Practices, Patients

by SHANNON BURKE and GREG PIERCE

FOR THE FIRST TIME most physicians no longer work in private practice, according to results of a study released by the American Medical Association (AMA) in May 2021. The AMA survey also showed the span of 2018 to 2020 saw the largest 2-year increase of doctors moving from small to large practices.

Further, results of a separate survey from the Physicians Foundation conducted in July 2020 found that 8% of physicians already had closed their practices 5 months into the COVID-19 pandemic and 43% had reduced staff—with more than half of these practices experiencing losses of at least one-fourth of their income.

Of the estimated 16,000 medical practices that closed in the early months of the pandemic, the majority (76%) were private practice owners or partners in small, independent practices, according to the survey. “The great majority of physicians will not leave medicine as a result of [COVID-19] health risks but may be more likely to leave for economic reasons,” the study authors wrote.

In the COVID-19 era, some of the most endangered practices are specialties that do not easily lend themselves to telehealth, or those that rely substantially on revenue generated from elective procedures, which are being curtailed because of avoidance of health care settings and staffing shortages, among other reasons.

Smaller practices may be less equipped to weather extreme economic pressures compared with hospital systems and large academic medical centers because they usually have fewer revenue streams and may be more susceptible to cash flow disruptions.

The proliferation of high-deductible insurance plans has made the patient the new payer. Out-of-pocket health expenses in the United States now surpass $400 billion annually, according to the Centers for Medicare & Medicaid Services. Results of an AMA report from July 2021 found that collection agencies last year held $140 billion in unpaid medical bills. And this number is low, measuring only delinquencies already sold off. Medical debt is America’s leading cause of bankruptcy, according to the National Consumer Law Center.

According to AMA data, 72% of physicians owned their practices in 1988. Now that number is down to 46%. In the face of so many challenges, what are those who value the independent practice of medicine to do?

Third-Party Patient Financing

To control their professional destiny, doctors must adapt and become as innovative with their financial instruments as they are with their medical instruments. Large health systems may be able to afford teams of financial professionals to focus on reimbursement and revenue, but in today’s lean environment, smaller practices are more likely to be focused on making enough revenue to meet a reduced payroll.

Some practices have adapted to cost-shifting trends by allowing patients to pay their bills in installments, but this type of direct patient financing can further stress revenue cycle management as payments once rendered in days are now stretched over months. And if patients don’t pay, practices must either absorb the losses or make a significant human and revenue investment to collect these costs.

Fortunately, small practices have new options to explore third-party patient financing to help patients plan for how they will pay their medical expenses—both expected and unexpected—with the practice receiving rapid payment and no-recourse financing from a financial partner. These services can be the difference between obtaining or forgoing care. Recognizing that every patient’s financial situation is as unique as their health.

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NOW ENROLLING: Clinical Trials for Lung Cancer with TIL Cell Therapy

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LN-145 (TUMOR INFILTRATING LYMPHOCYTES; TIL) is an investigational, personalized immunotherapy derived from the patient’s own immune cells.

KEY ELIGIBILITY CRITERIA:

- Diagnosis of Metastatic Non-small Cell Lung Cancer
- Disease progression after 1 or more lines of prior therapy which may have been a checkpoint inhibitor
- PD-L1 positive or negative status
- Tumors with EGFR, ALK, ROS mutations acceptable
- ECOG PS 0 – 1 (Fully active or able to carry out light work or activity)
- At least one tumor that can be safely removed by surgery for TIL and a second measurable tumor for response assessment

If these key eligibility criteria are met, you may be eligible to participate in our clinical study program. There are additional eligibility criteria that must be met and can only be assessed by a study physician.

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and effectiveness of this study has not been determined.

FOR MORE INFORMATION

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CLINICALTRIALS.GOV
Lung Trial: NCT04614103
Solid tumor trial NSCLC cohorts: NCT03645928

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by NITIN OHRI, MD, MS

THE IDEA TO PROVIDE wearable devices to my patients first came to me 6 years ago at a charity spinning event. A head and neck cancer nurse who was training for a marathon showed me her new Fitbit. It occurred to me that the data she was using to guide her training would be valuable for clinicians caring for individuals with cancer. Additionally, the use of wearable devices could also open the door to initiate effective dialogue and enhanced partnerships with our patients. Within a few months, my colleagues and I at Montefiore Einstein Cancer Center in the Bronx, New York, opened our first clinical trial using wearables to monitor patients receiving radiotherapy with concurrent chemotherapy.

More than one-quarter of the Bronx population lives in poverty,1 approximately 14% of residents have their bachelor’s degree, and anecdotally, few of our patients routinely engage with modern wearable devices. Therefore, Montefiore is well suited to both study the capacity for wearable devices to enhance cancer care and to identify barriers to wearable device use in an underprivileged patient population. The latter has also given us a gut check on the Digital Divide. We are proud to have developed a novel program utilizing wearables to monitor patients during radiotherapy in the Bronx.

ADDRESSING HEALTH INEQUITIES
The Digital Divide is the notion that as digital health becomes a routine component of patient care, we will see an exacerbation of outcome disparities across various subgroups in our society. Early work from our team suggests that low socioeconomic status (SES), rather than belonging to a racial or ethnic minority group, is the key predictor of patients’ inability to benefit from the digital health revolution.

We previously identified low SES as a risk factor for treatment interruptions and hospitalizations during radiotherapy.2 As a result of that research, we have navigator programs to assist patients through all steps of care, including enhanced support services such as social work and helping patients overcome obstacles to care such as transportation and housing. Though most of our patients are amenable to using a wearable device provided by our study team, we have observed that SES may affect our ability to collect digital health data.

STUDY STRUCTURE AND EARLY FINDINGS
For our wearable device trials, we selected a waterproof, user-friendly device that did not require charging. We also offered to download individuals’ step data during their routine clinic visits. This workflow allowed us to achieve a 94% data collection rate in our initial pilot study with approximately 40 subjects.3 In that first study (NCT02649569), we found a powerful association between daily step counts and hospitalization risk, with a 38% reduction in acute hospitalization risk for every 1000 steps per day. That finding has been reproduced in our follow-up trials, which now include more than 200 additional participants.

“We have seen that our patients appreciate the close monitoring and personalized care that wearable devices can facilitate. By better understanding barriers to the use of wearables, we can integrate digital health data into our electronic medical records and our routine clinic workflows.”

—NITIN OHRI, MD, MS
Importantly, we found that wearable devices provide new insights about patients’ functional status. Performance status, which is the most common measure clinicians use to try to quantify general well-being for patients with cancer, is highly subjective and only loosely correlates with clinical outcomes. We have discovered that activity data are superior to performance status as a predictor of hospitalizations, disease recurrence, and death.5

As an example, among patients who utilized wearables device while receiving chemoradiotherapy for advanced non-small cell lung cancer, study participants with low baseline activity levels—defined as having a step count average below the 25th percentile of age-matched healthy controls—were more likely than active patients to be hospitalized during the radiation therapy course (50% vs 9%, respectively; P = .004) and less likely to complete radiotherapy without a 1 week or more delay (67% vs 97%; P = .006).3 Further, patients with low baseline activity were 5 times more likely to experience disease recurrence or death. The median progression-free survival was 5.3 months vs 18.3 months (HR for inactivity, 5.10; P < .001).

We recently completed a study utilizing wearable devices to monitor patients receiving systemic therapy for metastatic malignancies, and we are seeing identical effects. It is just a matter of time before wearable device data are routinely incorporated in oncology clinics.

FUTURE DIRECTIONS
Incomplete wearable device data collection has been more common in our study subjects with low SES. Therefore, we are designing studies to better understand and address this phenomenon, focusing on issues such as internet availability at home and digital health literacy. These insights will be invaluable as we are leading numerous trials, including multi-institutional studies, where patients use wearable devices during cancer therapy. Study objectives include leveraging wearable device data to improve supportive care and prevent hospital admissions, as well as using wearables to understand the toxicity profiles of novel radiotherapy and immunotherapy combinations.

We are also evaluating our ability to collect data using more advanced devices in our patient population. One study will include patients treated at the New York Proton Center, which is the only proton therapy facility in New York and is operated by a consortium of city-based institutions that includes Montefiore, Memorial Sloan Kettering Cancer Center, and Mount Sinai Health System. This novel study will provide insight into how proton radiotherapy preserves patients’ functional status and quality of life compared with standard radiotherapy.

Future studies will expand the scope of how digital health technology can improve cancer patient care. This includes evaluating strategies that may bring more advanced devices to our patient population so we can understand the clinical significance of metrics beyond daily step count, such as heart rate variability.

We have seen that our patients appreciate the close monitoring and personalized care that wearable devices can facilitate. By better understanding barriers to the use of wearables, we can integrate digital health data into our electronic medical records and our routine clinic workflows (FIGURE 5). We look forward to reporting the outcomes of more of these trials and sharing lessons learned so that more individuals affected by cancer can benefit from the digital health revolution, regardless of SES.

REFERENCES
For appropriate patients faced with relapsed/refractory multiple myeloma

**FORGE AHEAD WITH A BOLD APPROACH**

**Target BCMA for RRMM**

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

**INDICATION**

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

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

**IMPORTANT SAFETY INFORMATION**

**WARNING: OCULAR TOXICITY**

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

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

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

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

Learn more at BLNREPHCP.com
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 169), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 or 4 keratopathy (n = 149), 38% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

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

Monitoring and Patient Instruction

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

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

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

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

5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

• Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.

• Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.

• Patients must be enrolled in the BLENREP REMS and comply with monitoring.

• Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.

• Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients.

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

5.4 Infusion-Related Reactions

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

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

5.5 Embryo-Fetal Toxicity

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

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

6 ADVERSE REACTIONS

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

• Ocular toxicity [see Warnings and Precautions (5.1)].

• Thrombocytopenia [see Warnings and Precautions (5.3)].

• Infusion-related reactions [see Warnings and Precautions (5.4)].

6.1 Clinical Trials Experience

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

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

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

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

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

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

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

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

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

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.
* Visual acuity changes were determined upon eye examination.
* Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
* Dry eyes included dry eye, ocular discomfort, and eye pruritus.
* Fatigue included fatigue and asthenia.

6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

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

Advise pregnant women of the potential risk to a fetus.

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

**Data**

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

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

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

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

- Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thromboembolism

- Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions

- Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].
- Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

- Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

Infertility

- Advise males and females of reproductive potential that BLENREP may impair fertility [see Use in Specific Populations (8.3)].

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Research Triangle Park, NC 27709

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Produced in USA.
Finding the Optimal Therapeutic Sequence for Advanced Hepatocellular Carcinoma

by TIMOTHY J. BROWN, MD; and THOMAS B. KARASIC, MD

FOR NEARLY A DECADE after the SHARP trial (NCT00105443) established sorafenib (Nexavar) as the standard of care for advanced hepatocellular carcinoma (HCC), progress in the development of systemic therapies for advanced HCC was frustratingly slow, with many clinical trials failing to improve outcomes vs sorafenib or placebo.1 Fortunately, there have been several breakthroughs in recent years that have rapidly shifted the treatment landscape for advanced HCC.

Since 2017, 9 drugs have received an FDA approval for HCC. Most importantly, an improved frontline regimen for advanced HCC has been solidly established with the publication of results from the IMbrave150 trial (NCT03434379).2 For patients with preserved liver function and no active esophageal varices, the combination of the PD-L1 inhibitor atezolizumab (Tecentriq) and the VEGF inhibitor bevacizumab (Avastin) is the current frontline standard on the basis of improved overall survival (OS), progression-free survival (PFS), objective response rate, and toxicity profile compared with sorafenib.2

Although atezolizumab and bevacizumab has become the standard initial therapy for eligible patients with advanced HCC, several ongoing phase3 trials evaluating immunotherapy combinations in the frontline setting are expected to publish their results in the near future (COSMIC-312 [NCT03755791], LEAP-002 [NCT03713593], HIMALAYA [NCT03298451], CheckMate 9DW [NCT04039607], and RATIONALE-301 [NCT03412773], among others).3 Recently, it was announced that the HIMALAYA trial, in which investigators are evaluating tremelimumab and durvalumab [Imfinzi] vs sorafenib in first-line untreated HCC, met its primary end point of improved OS. COSMIC 312, which is examining the efficacy of cabozantinib [Cabometyx] and atezolizumab vs sorafenib, is not expected to improve OS vs sorafenib based on an interim analysis.4,5

If multiple frontline trials are positive, it may prove difficult to choose between frontline immunotherapy combination regimens based solely on cross-trial comparisons. For now, atezolizumab and bevacizumab is clearly the best available frontline option for systemic therapy for eligible patients.

ADDRESSING AN UNMET NEED IN HCC

Despite the unprecedented improvements in OS and PFS observed with atezolizumab and bevacizumab, many patients will invariably experience progressive disease. For patients experiencing progressive disease, no definitive prospective data are available to guide decisions regarding subsequent treatments. Given the timelines required for the design and execution of clinical trials, these data may not be available for years.

Standard clinical practice is to evaluate those who are still eligible for systemic therapy for clinical trial enrollment at the time of progression. However, without an available clinical trial, the approach to therapy following progression on atezolizumab and bevacizumab is up for debate and guided mostly by expert opinion extrapolated from prior experience.

The American Society of Clinical Oncology (ASCO) issued formal guidelines in 2020 recommending second-line therapy individualized to patient and clinician factors, with the caveat that data for second-line therapy in clinical trials was only following progression with sorafenib (TABLE).6

Recognizing the lack of high-quality data to guide practice in the second-line setting after atezolizumab and bevacizumab, current treatment paradigms for second-line systemic therapy include shifting all previously approved and available first-line therapies, such as sorafenib and lenvatinib (Lenvima), to the second line or simply forgoing prior first-line therapies and moving forward with previously approved second- and third-line therapies (eg, cabozantinib and regorafenib [Stivarga]).

First-line tyrosine kinase inhibitors (TKIs) exert their anticancer activity primarily through VEGF inhibition. Second-line TKIs
target additional established VEGF-resistance pathways—MET for cabozantinib, TIE2 for regorafenib—and have proven efficacy after prior anti-VEGF therapy with sorafenib. Conversely, over the course of a decade of investigators evaluating other VEGF TKIs vs sorafenib in trials, only lenvatinib produced a positive result, supporting the current place of sorafenib and lenvatinib as the initial TKIs regardless of prior therapy. It is not likely that clinical trials will be designed to empirically address the optimal sequencing of TKIs. Further, bias by indication will confound all retrospective analyses that will emerge attempting to answer this question.

**REEVALUATING THE CONTINUED ROLE OF STANDARD CARE**

There are early retrospective data suggesting multikinase inhibitors such as sorafenib and lenvatinib still retain activity after progression on atezolizumab and bevacizumab. For example, in results from a multicenter retrospective analysis of Asian patients, partial responses were only seen with lenvatinib; most patients on sorafenib having stable disease. In this study, median OS from date of initiation of second-line therapy with TKIs following progression on atezolizumab and bevacizumab was 14.7 months and median PFS was 3.4 months. The overall response rate was 6.1% among the 49 treated patients.

Although these data are limited by the study design, they do provide preliminary reassurance that TKIs retain relevant activity after atezolizumab and bevacizumab. For patients experiencing progressive disease who are not enrolling in clinical trials, our practice has been to initiate second-line therapy with lenvatinib given the improved PFS and decreased rates of important toxicities including diarrhea and hand-foot syndrome when compared to sorafenib.

Recognizing the shortcomings in the available data, the ASCO guideline committee only issued an informal consensus recommendation for second-line therapy with a TKI such as sorafenib and lenvatinib, but also noted that cabozantinib and regorafenib may be offered. Ramucirumab (Cyramza) is also an option for patients with α-fetoprotein 400 ng/mL or higher, but there is concern that ramucirumab may not retain as much activity as a TKI after progression on bevacizumab given the highly similar mechanisms of action of ramucirumab and bevacizumab. The evidence quality for these recommendations was weak and the strength of the resulting recommendation was low.

**ALTERNATIVE OPTIONS**

The role of subsequent immunotherapy following progression on atezolizumab and bevacizumab remains unsettled. The combination of nivolumab and ipilimumab (Yervoy) was approved after sorafenib based on prolonged survival in a phase 2 cohort of the CheckMate 040 study (NCT01638878), but all patients in this study did not receive prior immunotherapy.

In melanoma, a response rate of 13% was reported among 97 patients who received ipilimumab alone after prior PD-1 blockade in results of the KEYNOTE-006 trial (NCT01866319), similar to the response rate of 29% among 70 immunotherapy-naive patients who received ipilimumab and pembrolizumab together in a phase 2 trial (NCT02743819). A response rate that is approximately half of that was seen with dual checkpoint blockade (58%) in naïve patients.

Whether similar retreatment efficacy with immunotherapy holds in HCC remains unknown, but with response rates of only 7% with tremelimumab monotherapy and 30% with nivolumab and ipilimumab in immunotherapy-naïve patients, the response rate is likely to be low following rechallenge with dual checkpoint blockade after atezolizumab and bevacizumab and toxicity can be significant. For these reasons, we favor second-line TKI therapy in eligible patients, with immunotherapy rechallenge reserved for the third- or later-line settings.

Furthermore, a more prolonged and deeper initial response to front-line atezolizumab and bevacizumab is more suggestive of immune activation than VEGF response; we primarily consider immunotherapy rechallenge in those who experienced an objective response to atezolizumab and bevacizumab or experienced disease stability for at least 6 months.

Another important question that remains is how to approach patients with advanced HCC who are not eligible for atezolizumab or bevacizumab. Contraindications to this regimen include severe active autoimmune disease, hepatitis C, and hypertension.

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**TABLE. ASCO Recommendations for Advanced HCC**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence type (quality)</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab plus bevacizumab may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG performance status 0 to 1, and following management of esophageal varices, when present, according to institutional guidelines</td>
<td>Evidence based, benefits outweigh harm (moderate-high)</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Contraindications:</strong> Where there are contraindications to atezolizumab and/or bevacizumab, TKIs sorafenib or lenvatinib may be offered as first-line treatment of patients with advanced HCC, Child-Pugh class A, and ECOG performance status 0 to 1</td>
<td>Evidence based, benefits outweigh harm (moderate)</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Second-line setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following first-line treatment with atezolizumab plus bevacizumab, second-line therapy with a TKI (ie, sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended</td>
<td>Informal consensus, benefits may outweigh harms (low)</td>
<td>Weak</td>
</tr>
<tr>
<td>Following first-line treatment with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥ 400 ng/mL), or atezolizumab plus bevacizumab may be recommended for appropriate candidates</td>
<td>Informal consensus, benefits may outweigh harms (low to moderate)</td>
<td>Weak</td>
</tr>
<tr>
<td>Following first-line therapy with sorafenib or lenvatinib, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates</td>
<td>Informal consensus, benefits may outweigh harms (low)</td>
<td>Weak</td>
</tr>
</tbody>
</table>

AFP, α-fetoprotein; ASCO, American Society of Clinical Oncology; HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor.
solid organ or allogenic stem cell transplant, recent myocardial infarction or stroke, active and untreated esophageal varices, uncontrolled hypertension, nonhealing wounds, and congestive heart failure. For patients with contraindications to anti-angiogenic therapy, the use of the TKIs sorafenib and lenvatinib would also be contraindicated.

National Comprehensive Cancer Network guidelines support the use of nivolumab in this setting based on findings from CheckMate 459. Some patients may also prefer to avoid intravenous therapies and opt for oral agents, especially during the COVID-19 pandemic. Options for these patients include the previous standard frontline TKIs sorafenib or lenvatinib. Lenvatinib is our preferred option for those with preserved liver function (Child-Pugh A) on the basis of data from the REFLECT trial (NCT01761266), which showed improved PFS and overall response rates. There are also some tradeoffs with adverse effects; lenvatinib is associated with increased fatigue, hypertension, proteinuria, and anorexia, but less diarrhea and hand-foot syndrome compared with sorafenib.

UNCOVERING PATHS FORWARD FOR POOR LIVER FUNCTION

Finally, there remains a paucity of data on the management of patients with Child-Pugh B liver function. These patients are typically excluded or are under-represented in clinical trials for advanced HCC, yet they represent a significant proportion of patients seen in routine clinical practice. Notably, these patients were not included in IMbrave150 because of concerns about the bleeding risk associated with bevacizumab.

Prospective phase 2 cohorts have demonstrated safety and efficacy of both nivolumab and sorafenib in patients with Child-Pugh B cirrhosis. The ASCO guidelines specifically do not offer recommendations for this group of patients, instead advising a multidisciplinary discussion for the management of these patients and a cautious approach to systemic therapy.

More recently, retrospective data from the Veterans Affairs showed improved OS with nivolumab compared to sorafenib in Child-Pugh B cirrhosis, though prospective comparative data in patients with Child-Pugh B cirrhosis is sorely lacking.

Our practice is to offer these patients nivolumab initially and consider sorafenib at progression if liver function permits.

In conclusion, combination atezolizumab and bevacizumab is the current standard for frontline treatment for eligible patients with advanced HCC, although additional frontline immunotherapy combinations will likely become available within the next year. For patients who progress after initial atezolizumab and bevacizumab, no defined treatment paradigm yet exists, though TKIs are used most. The utility of immunotherapy rechallenge remains uncertain. Over the next 1 to 2 years as additional frontline immunotherapy combinations emerge, the development of consensus guidelines will be critical to guide practicing oncologists through the expanding array of treatment options, a fortunate problem few might have predicted just a few short years ago.
Novel Immunotherapy Combos Target TIM-3 and PD-1/PD-L1 Networks

by ANITA T. SHAFFER

**THE IMMUNE CHECKPOINT TIM-3**

is shaping up to be a viable target for designing therapies for patients with non-small cell lung cancer (NSCLC) and other malignancies, according to a growing body of early scientific and clinical data. Investigative efforts so far are focusing on pairing novel agents directed at TIM-3 activity with PD-1/PD-L1 immune checkpoint inhibitor (ICI) therapy.1,2

The research involving TIM-3 comes amid continuing efforts to boost the efficacy of ICI immunotherapy. Although PD-1/PD-L1 ICIs have improved outcomes for patients in a range of tumor types, primary and acquired resistance represents a significant unmet need. Investigators are exploring ICI combinations, including regimens involving novel immune checkpoints such as TIM-3, as a means of increasing response rates.3,4

The potential for leveraging TIM-3 for anticancer therapy is being tested in early studies in several solid malignancies, with many of the trials exploring dual combination of ICIs aimed at TIM-3 and PD-1/PD-L1 immune checkpoints. Other approaches include bispecific antibodies that simultaneously target TIM-3 and PD-1 (TABLE).

In NSCLC, TIM-3 is among the intriguing emerging targets in development, according to experts who participated in Molecular Targets on the Horizon in Non–Small Cell Lung Cancer OncLive® Scientific Interchange & Workshop, a panel discussion held on September 27.

“The theory here is that you can overcome I/O [immuno-oncology] resistance with a combination of a TIM-3 antibody with a PD-1/PD-L1 antibody,” Fred R. Hirsch, MD, PhD, said during the program. “We don’t have advanced clinical data...but I think we will see more and more of this target in the future.”

Hirsch, a longtime biomarker expert in the lung cancer field, is executive director at the Center for Thoracic Oncology in The Tisch Cancer Institute at Mount Sinai and the Joe Lowe and Louis Price Professor of Medicine (Hematology and Medical Oncology) at Icahn School of Medicine at Mount Sinai, both in New York, New York.

**PROGNOSTIC IMPLICATIONS OF TIM-3 EXPRESSION**

TIM-3, which stands for T-cell immunoglobulin and mucin domain 3, is a member of a family of coinhibitory receptors that help regulate immune responses. First described in 2002, TIM-3 is a cell-surface glycoprotein that can be expressed both on tumor cells and multiple types of immune cells.1,4,5

Hirsch noted that TIM-3 particularly is expressed on CD4-positive and CD8-positive T cells and often is coexpressed with other immune checkpoints such as PD-1 and TIGIT.

Investigators have identified 4 ligands that interact with TIM3: galectin-9, phosphatidylserine, HMGB1, and CEACAM1.6 Galectin-9 is considered TIM-3’s main ligand; binding of TIM-3 with this ligand inhibits an immune response by promoting cell death in TIM3-expressing T cells.2 TIM-3 also is upregulated on regulatory T cells, which hampers effector T cell functions (FIGURE). Specifically, TIM-3 overexpression contributes to T-cell exhaustion, which is characterized by a loss of T-cell effector functions, expression of inhibitory receptors, and alterations in transcriptional functions.2

Hirsch noted that TIM-3 expression has a “complex biology” that negatively affects the immune system. “It is demonstrated...
preclinically that TIM-3 expression leads to dysfunctional lymphocytes and a dysfunctional immune reaction,” he said.

Findings from a meta-analysis published in *Frontiers in Oncology* in August 2020 illustrate the prognostic impact of TIM-3 expression, according to Hirsch. “TIM-3 protein expression is related to poor overall survival, poor outcomes, and increased capacity of metastasis,” he said. “And that is certainly a bad prognostic indicator.”

The meta-analysis was based on findings involving 3072 patients with solid tumors who were treated during 21 studies reporting results from 2012 to 2019 from China, Japan, Korea, and Poland. Thirteen tumor types were represented in the study populations. TIM-3 protein expression was evaluated via immunohistochemistry (IHC) on tumor cells and/or tumor-infiltrating lymphocytes (TILs).

For the entire study population, TIM-3 overexpression correlated with poor overall survival (HR, 1.73; 95% CI, 1.39-2.15; P < .001). Additionally, TIM-3 expression was associated with positive lymph node metastases (N+ vs N−; OR, 1.59; P = .013), higher tumor grade (G2-3 vs G1; OR, 1.68; P = .002), and PD-L1 expression (PD-L1 high vs PD-L1 low; OR, 3.26; P < .001).

In terms of tumor types, elevated TIM-3 protein expression was a negative predictor of overall survival (OS) for patients with NSCLC, gastric cancer, esophageal squamous cell carcinoma, and other cancers but not for participants with breast cancer. In a further analysis, investigators analyzed data on TIM-3 mRNA expression for patients with NSCLC, gastric cancer, and breast cancer from a public database and found that the results aligned with their findings on the prognostic impact based on protein expression. High TIM-3 mRNA expression was significantly correlated with poor OS outcomes in patients with NSCLC (HR, 1.46; P < .001) and gastric cancer (HR, 1.41; P = .0038) but not breast cancer (HR, 0.79; P = .51).

Investigators also examined the impact of TIM-3 protein expression on disease-free survival (DFS) outcomes based on findings from 7 studies involving 1243 patients. For the overall population, the data showed that TIM-3 expression did not correlate with DFS (HR, 1.39; 95% CI, 0.75-2.57; P = .297). However, elevated TIM-3 expression was significantly associated with shorter DFS in patients with NSCLC (HR, 2.40; P < .001).

Another study finding showed a difference in the impact of TIM-3 expression on tumor cells vs TILs. TIM-3 overexpression was significantly associated with worse OS outcomes on tumor cells (HR, 2.10; P < .001) compared with TILs (HR, 1.34; P = .105).

Investigators noted that TIM-3 expression on tumor cells appears to have greater prognostic value than levels on TILs but that further research is needed to verify this finding. The table below provides an overview of clinical development of combinations targeting TIM-3 and PD-1 pathways.
this signal. The authors also said that because most of the participants whose data were examined live in East Asia, similar analyses should be conducted on results from European patients. Another limitation involved the calculation of TIM-3 IHC expression; the antibodies and cut-off values differed among studies included in the meta-analysis.\textsuperscript{7}

**DUAL BLOCKADE STRATEGIES**

In 2010, investigators established the negative impact on the immune system of upregulated TIM-3 and PD-L1 coexpression on melanoma specimens and suggested that a combination blockade strategy would be effective.\textsuperscript{8} Both TIM-3 and PD-L1 overexpression are markers of T-cell exhaustion; inhibiting both may result in a restoration of T-cell proliferation and cytokine production, thus generating an immune response.\textsuperscript{9}

Results of in vitro studies show that combining TIM-3 inhibition with a PD-1/PD-L1 antibody increases production of interferon $\gamma$. \textsuperscript{2,9} “If you combined a blockade of TIM-3, which is the same mechanism as with PD-1/PD-L1, you actually see quite a lot of synergy,” Hirsch said. “…You see improvement of lymphocyte function and penetration and immune capacity.”

Early data from several clinical trials are encouraging, investigators say. In 2018, investigators reported the first findings from combination therapy with a TIM-3-directed antibody and a PD-1 ICI, cobolimab (TSR-022) and dostarlimab-gxly (Jemperli), respectively, for patients with NSCLC who participated in the first-in-human multicohort phase 1 AMBER study (NCT02817633).\textsuperscript{10}

At the time of data cutoff, 39 patients with NSCLC whose disease had progressed after anti-PD-1 therapy had received cobolimab at either 100 mg or 300 mg plus a fixed dose of dostarlimab at 500 mg. Of the 14 patients who received the lower dose of cobolimab, 11 were evaluable for response; 1 had a confirmed partial response by immune-related RECIST criteria and 3 had stable disease. Of the 25 patients who received the higher dose of cobolimab, 20 were evaluable for response; 3 had confirmed partial responses and 8 had stable disease. All objective responses were among patients with PD-L1 tumor proportion scores of 1% or more.

Overall, the AMBER study, which seeks to enroll 369 participants, includes 2 parts. Part 1 comprises 8 experimental arms evaluating cobolimab as monotherapy and in combination with dostarlimab, the PD-1 inhibitor nivolumab (Opdivo), the anti-LAG-3 antibody TSR-033, or chemotherapy in patients with advanced solid tumors. In part 2, there are separate cohorts testing cobolimab as monotherapy or in combination with dostarlimab in patients with NSCLC, melanoma, and colorectal cancer.

Investigators said the combination regimen was well tolerated across multiple dosing levels and that the responses showed the strategy is worth pursuing.\textsuperscript{11} However, they recommended increasing the dose of cobolimab to 900 mg for the NSCLC expansion cohort after analysis demonstrated that the 300-mg dose was inadequate for maintaining a maximal pharmacodynamic effect.\textsuperscript{10}

Meanwhile, triplet therapy with cobolimab plus dostarlimab and docetaxel is being evaluated in patients with advanced NSCLC in the phase 2/3 COSTAR Lung study (NCT04655976). Another experimental cohort is testing dostarlimab plus docetaxel, and the comparator arm is evaluating docetaxel monotherapy.

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**Molecular Targets on the Horizon in Non–Small Cell Lung Cancer**

*OncLive® Scientific Interchange & Workshop*

**PROGRAM**

7 lung cancer experts discuss new data on emerging targets

**TARGETS**

- CEACAM5
- TROP-2 expression
- HER3 expression
- TIGIT
- TIM-3
- Tumor-infiltrating lymphocytes

**FACULTY**

**Moderator**

Paul A. Bunn Jr, MD  
University of Colorado School of Medicine

**Panelists**

Lowell L. Hart, MD, FACP  
Florida Cancer Specialists & Research Institute

Karen L. Kelly, MD  
UC Davis Comprehensive Cancer Center

Fred R. Hirsch, MD, PhD  
The Tisch Cancer Institute at Mount Sinai

Corey J. Langer, MD, FACP  
Abramson Cancer Center

Xiuning Le, MD, PhD  
The University of Texas MD Anderson Cancer Center

Sandip P. Patel, MD  
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As these trials continue, dostarlimab has moved into the ranks of approved therapies. In separate decisions in 2021, the FDA granted dostarlimab accelerated approvals for adult patients with mismatch repair-deficient recurrent/advanced solid tumors or endometrial cancer that has progressed on or following prior treatment who have no satisfactory alternative treatment options.12

In other early findings, investigators reported that the combination of sabatolimab (MBG453), a TIM-3 antibody, and spartalizumab (PDR001), a PD-1 ICI, generated partial responses lasting between 12 and 27 months among 6% of 86 patients with advanced solid tumors who received the regimen in an ongoing phase 1/2 study (NCT02608268). The responders included 2 patients with colorectal cancer and 1 each with NSCLC, malignant perianal melanoma, and small cell lung cancer. No responses were observed with sabatolimab monotherapy. The most common treatment-related adverse effect was fatigue, which was reported in 9% of those who received monotherapy and in 15% who had the combination.13

Another experimental TIM-3 antibody, LY3321367, was tested as monotherapy and in combination with LY3300054, a PD-L1 inhibitor, in patients with advanced cancers during a phase 1 study (NCT03099109). In April 2021, investigators reported that the agent had an acceptable safety profile but exhibited “only modest antitumor activity.” In the NSCLC monotherapy expansion cohort, the objective response rate (ORR) was 0% among 23 patients who were refractory to PD-1/PD-L1 therapy and 7% among 14 prior ICI responders. In the combination expansion cohorts, the ORR was 4%.14 The study is active but no longer recruiting participants, according to ClinicalTrials.gov.

**BGB-A425 Plus Tislelizumab**

From the roster of novel regimens in development, Hirsch highlighted an ongoing phase 1/2 study (NCT03744468) testing the novel TIM-3 antibody BGB-A425 in combination with tislelizumab, a PD-1 inhibitor.

In the phase 1 dose-escalation phase, patients with locally advanced or metastatic unresectable solid tumors will receive BGB-A425 IV at increasing dosing levels ranging from 2 mg to 800 mg plus tislelizumab at 200 mg IV. The primary end points are safety, tolerability, and the identification of the recommended phase 2 dose.

In the phase 2 stage, the combination will be tested in separate cohorts of patients with recurrent or metastatic head and neck squamous cell carcinoma, extensive-stage NSCLC, or advanced gastric/gastroesophageal junction cancer. The primary end point is the objective response rate.9

Investigators are seeking to recruit up to 42 patients from Australia and the United States to participate in phase 1 of the study. To be eligible, patients must have previously received standard systemic therapy, if available, or been unable or unwilling to undergo such treatment. The goal for phase 2 is to enroll up to 120 patients from Asia, Australia, and the United States. For these disease-specific cohorts, patients must have advanced or metastatic disease with 1 or more measurable lesions that has progressed after the most recent treatment.

Although BGB-A425 is a novel agent, tislelizumab is becoming an established part of anticancer therapy. Tislelizumab is approved in China for 5 indications including several first-line NSCLC settings, according to BeiGene Ltd, a pharmaceutical company based in Beijing, China, that is developing that drug, as well as developing both drugs in the regimen.15 The company is collaborating with Novartis to develop tislelizumab in North America, Europe, and Japan.15,16 In the United States, the FDA is reviewing a biologics license application for tislelizumab for treating patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma after prior systemic therapy. The agency is scheduled to decide on the application by July 12, 2022.16

**Other Partners**

In hematologic malignancies, investigators are studying whether there is a role for combining TIM-3 inhibitors with other agents besides ICIs. In May 2021, the FDA granted a fast track designation for sabatolimab in combination with hypomethylating agents for the treatment of adult patients with myelodysplastic syndromes (MDS) defined as high or very high risk on the Revised International Prognostic Scoring System.17

Novartis, the company developing the drug, is exploring the efficacy of sabatolimab as part of different combination therapies in patients with MDS and acute myeloid leukemia (AML). The development program includes the phase 2 STIMULUS-MDS1 (NCT03946670) and STIMULUS-MDS3 (NCT04812548) studies and the phase 3 STIMULUS-MDS2 (NCT04266301) study in MDS, as well as the phase 2 STIMULUS-AML1 study (NCT04150029) in AML.

**LINE OF THERAPY IN NSCLC**

The studies of combination TIM-3 and PD-1/PD-L1 inhibitors underway in NSCLC are recruiting patients who already have received at least 2 lines of therapy. Paul A. Bunn Jr, MD, who served as moderator for the OncLive® program, wondered about the rationale for not testing the combination in upfront settings, where the regimen might be more effective. He also questioned whether a patient who progressed on ICI therapy would respond to repeat administration of an ICI with an added therapy.

Bunn, a 2014 Giants of Cancer Care® award winner in the lung cancer category, is the James Dudley Chair in Cancer Research and a distinguished professor of medicine-medical oncology at the University of Colorado School of Medicine in Aurora.

Hirsch agreed that the combination therapy is a candidate for first-line settings but that investigators are still seeking to establish “acceptable safety data” with early-phase studies. “The primary goal so far in this drug development has been to overcome I/O resistance,” he said. “...First-line studies are traditionally in later lines. We might see it in the future when we have a clear picture of the safety and the doses.”

With regard to biomarkers, Hirsch said IHC scoring approaches are “still on a very premature level of development” compared with other immunotherapies and that much more work is needed.
OncLive On Air® is a podcast from OncLive®, which provides oncology professionals with the resources and information they need to provide the best patient care. In both digital and print formats, OncLive® covers every angle of oncology practice, from new technology to treatment advances to important regulatory decisions.

In our exclusive interview, Kathleen Moore, MD, provides perspectives on the ongoing research with the combination of VS-6766 and defactinib in ovarian cancer and the potential role for the treatment in clinical practice.
Investigators Navigate the Complicated Treatment Landscape of Chemotherapy-Induced Neutropenia

by CHRISTINA T. LOGUIDICE

ADVANCES IN THE TREATMENT of solid tumors and hematologic malignancies have resulted in the development of therapeutics regimens that can be administered at various points in a patient’s care. However, as patients’ disease progresses, adverse effects (AEs) from initial standards of care or second- or later-line may limit the ability of a patient to pursue additional treatments. Neutropenia is a common complication of chemotherapy that increases the risk of serious infections and fever and may require adjustments to patients’ chemotherapy schedules, potentially affecting their early and long-term outcomes. “It can be quite challenging in clinics to [treat], prevent, anticipate, and then keep patients on track in terms of their curative chemotherapy or therapy that’s helping to extend life and keep their symptoms under control,” Rita Nanda, MD, said during a recent OncLive Peer Exchange®.

Nanda was joined by a panel of breast cancer experts to discuss this high-stakes complication, which may be encountered more frequently in patients with breast cancer than other tumor types as risk of neutropenia tends to increase with increasing treatment lines. “We see it in breast cancer because we’re [treating] patients in the sixth-, seventh-, or eighth-line setting,” Tiffany A. Traina, MD, explained. During their discussion, the panelists shared their experiences with chemotherapy-induced neutropenia (CIN) and provided insights on its risk factors, when to intervene, use of granulocyte colony-stimulating factors (G-CSFs), and the unique challenges associated with these agents.

DEFINING CIN
A patient is generally considered to have CIN when their absolute neutrophil count (ANC) count is less than 2000 cells/µL. This toxicity is then further classified into grades based on severity (TABLE 1). Nanda said she considers CIN to be any ANC level that would preclude her from providing a patient with their planned treatment. In most cases, she said this is an ANC level of 1000 cells/µL or less. It is at this threshold when the most severe form of neutropenia, febrile neutropenia, may manifest. The National Cancer Institute’s Common Terminology Criteria for Adverse Events version 5.0 characterizes chemotherapy-induced febrile neutropenia (CIFN) as an ANC level less than 1000 cells/µL and a single temperature of higher than 38.3 °C (101 °F) or a sustained temperature of at least 38 °C (100.4 °F) for more than 1 hour.

RISK FACTORS FOR CIN
“It’s not always entirely predictable in whom [CIN] is going to occur,” William J. Gradishar, MD, said. He explained that there can be variability, even among patients receiving the same treatments.
All 3 (NCT02181101), 3 SNPs in HMMR in the phase 3 SUCCESS-A trial were treated with 5-fluorouracil, being used," she said. For example, in a neutropenia, depending on the regimen polymorphisms] that may predispose to ture around certain SNPs [single nucleotide increasing treatment lines. “There is litera - compromised bone marrow, and more advanced disease and/or more white blood cell counts, presence of more advanced disease and/or more compromised bone marrow, and increasing treatment lines. “There is literature around certain SNPs [single nucleotide polymorphisms] that may predispose to neutropenia, depending on the regimen being used,” she said. For example, in a study of patients with breast cancer who were treated with 5-fluorouracil, epirubicin, and cyclophosphamide in the phase 3 SUCCESS-A trial (NCT02181101), 3 SNPs in HMMR were found to be significantly associated with neutropenia. All 3 of these SNPs were transexpression quantitative trait loci for the expression of TNFSF13B, encoding the cytokine B-cell activating factor. However, Traina said that SNP find - ings are not yet actionable but the hope is that they may eventually lead to the identifi - cation of biomarkers predictive of CIN risk. The panelists noted that although CIFN is uncommon in their practices, it still occurs. A risk factor for CIFN is the use of corticosteroids, with longer-term use and more recent use of these agents reported to increase the risk of CIFN 3-fold and 2-fold, respectively. Additionally, certain dermatologic and mucosal conditions (eg, gastritis, dermatitis, psoriasis), as well as the use of intravenous antibiotics, but not oral antibiotics, before chemotherapy, have been associated with a higher risk of CIFN during the first chemotherapy cycle. It has been suggested that these factors should be consid - ered in prophylaxis use and CIFN prediction modeling.

### CIN PROPHYLAXIS RECOMMENDATIONS

The National Comprehensive Cancer Network (NCCN) guidelines recommend that all patients with solid tumors and nonmyeloid malignancies be evaluated for their risk of CIFN before their first chemotherapy cycle. The risk assessment should consider patients’ disease; chemotherapy regimen, including intensity (eg, high-dose, dose-dense, or standard-dose therapy); individual patient risk factors; and treatment intent (ie, curative vs palliative). Based on these findings, patients are classified into a high-, intermediate-, or low-risk category, which guides the use of prophylactic G-CSFs (TABLE 2).

Traina explained that these are recommenda - tions for primary prophylaxis. “Obviously, we’re all very comfortable once you’ve gone to treat a patient on, say, day 1 of a cycle, and they present with limit - ing neutropenia, then incorporating growth factor in that secondary prophylaxis setting, [which] is often preferred to keep patients on schedule at an appropriate dose and intensity,” she said.

Though the NCCN guidelines provide guidance on preventing CIFN following the first round of chemotherapy, they do not address CIFN risk after patients start chemotherapy. "It’s important for us to understand when patients are at their greatest risk for CIN, which is after they start chemother - apy. That’s something our patients also want to know, in terms of what their risk is if they’re going to travel or work," Hope S. Rugo, MD, FASCO, said.

Rugo explained that with most regimens neutropenia occurs 7 to 10 days after chemotherapy is adminis - tered, though risk of CIN may be prolonged when drugs with a longer half-life are used, such as platinum agents. "We worry a lot about infections when [a patient] has grade 4 neutropenia with a neutrophil count fewer than 500 per µL, whereas we’ll see patients with a neutrophil count of 980 per µL, which is fewer than 1000 per µL but not worri - some.…There’s some risk, but with fewer than 500 per µL there’s an even greater risk," she said.

Nanda said clinicians should have a low threshold on when to integrate prophylaxis into their regimens, particularly during the COVID-19 pandemic. “In this era of COVID-19, we need to be aggressive about trying to prevent neutropenia and neutro - penic fevers because hospitals are not great places for our patients to be right now, and emergency departments are even more challenging [environments]. Preventing neutropenia and preventing neutropenic fevers is even more critical for our patients,” she emphasized.

### USING GROWTH FACTORS IN CLINICAL PRACTICE

The panelists explained that the support - ive measures used today, such as growth factors, have helped eliminate or at least

<table>
<thead>
<tr>
<th>Risk of CIFN</th>
<th>Risk classification</th>
<th>Prophylaxis recommendation</th>
</tr>
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<tbody>
<tr>
<td>&gt;20%</td>
<td>High</td>
<td>Use G-CSFs</td>
</tr>
<tr>
<td>10% to 20%</td>
<td>Intermediate</td>
<td>Consider G-CSFs</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>Low</td>
<td>No G-CSFs</td>
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CIFN, chemotherapy-induced febrile neutropenia; G-CSFs, granulocyte colony-stimulating factors; NCCN, National Comprehensive Cancer Network.

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traina noted that there are many patient- and disease-related risk factors for CIN, including older age (≥ 65 years), compromised organ function (eg, elevated bilirubin levels), low body surface area or body mass index, low baseline white blood cell counts, presence of more advanced disease and/or more compromised bone marrow, and increasing treatment lines. “There is literature around certain SNPs [single nucleotide polymorphisms] that may predispose to neutropenia, depending on the regimen being used,” she said. For example, in a study of patients with breast cancer who were treated with 5-fluorouracil, epirubicin, and cyclophosphamide in the phase 3 SUCCESS-A trial (NCT02181101), 3 SNPs in HMMR were found to be significantly associated with neutropenia. All 3 of these SNPs were transexpression quantitative trait loci for the expression of TNFSF13B, encoding the cytokine B-cell activating factor. However, Traina said that SNP find - ings are not yet actionable but the hope is that they may eventually lead to the identifi - cation of biomarkers predictive of CIN risk. The panelists noted that although CIFN is uncommon in their practices, it still occurs. A risk factor for CIFN is the use of corticosteroids, with longer-term use and more recent use of these agents reported to increase the risk of CIFN 3-fold and 2-fold, respectively. Additionally, certain dermatologic and mucosal conditions (eg, gastritis, dermatitis, psoriasis), as well as the use of intravenous antibiotics, but not oral antibiotics, before chemotherapy, have been associated with a higher risk of CIFN during the first chemotherapy cycle. It has been suggested that these factors should be consid - ered in prophylaxis use and CIFN prediction modeling.

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### USING GROWTH FACTORS IN CLINICAL PRACTICE

The panelists explained that the support - ive measures used today, such as growth factors, have helped eliminate or at least
significantly reduce the risk of many of the toxicities observed in the past, such as mouth sores and typhlitis. “The most common symptoms we see are the sequela of chemotherapy, low-grade fevers, or flu-like symptoms,” Gradishar said. “The typical AEs that would have been more common at the early part of our careers are infrequent.” Nevertheless, he warned that there are rare patients who may still experience profound neutropenia in the immediate period after chemotherapy before their blood counts recover, which can be catastrophic.

Traina recently encountered such a patient, a woman in her late 60s treated with docetaxel/cyclophosphamide (TC) in the adjuvant setting. She said the patient was hospitalized with neutropenic colitis after her first treatment cycle. Based on her experience, Traina said she is very sensitive to risk factors and using growth factors as prophylaxis for any patient with a high-risk feature.

Gradishar agreed and indicated that, although chemotherapy regimens have improved and become more tolerable overall, there are still regimens that warrant the use of G-CSF prophylaxis, including some requiring a long-acting G-CSF such as pegfilgrastim (Neulasta). “With TC we [give pegfilgrastim]. With AC [doxorubicin hydrochloride/cyclophosphamide], we [give it] every other week. [With] weekly paclitaxel, we don’t. We don’t use TAC [docetaxel/ doxorubicin hydrochloride/cyclophosphamide],” he explained.

The panelists also noted differences in their G-CSF prophylaxis practices in the curative/adjuvant setting vs the metastatic setting. Rugo said she still tends to use growth factors in the metastatic setting “to keep [patients] on schedule in part because they do better and secondly because it’s a nightmare to reschedule everybody all the time,” but that they might change the schedules to every other week.

Gradishar and Traina both said they tend to be less rigid about patients staying on their chemotherapy schedules in the metastatic setting because the focus is more on palliation. “There’s a real inconvenience aspect to self-injection or having to come into the clinic for daily growth factor injection,” Traina said. “In the palliative setting, that’s not where I want my patients spending their time. I don’t want them to be in the hospital or the clinic. I’m with [Dr Gradishar], adjusting schedules and does perhaps a little more liberally in that setting.”

Nanda said that she also considers patients’ past experiences to determine the need for G-CSF in the metastatic setting. “If I have patients who’ve been on chemotherapy drugs that generally aren’t associated with needing growth factor but they needed it, then a lot of times I will preventively use it when they move on to subsequent lines of therapy,” Nanda said. “There are cases in which I’ll even preventively use it in the advanced cancer setting, particularly for patients who have a heavy disease burden and have struggled with therapies in the past that most [patients] don’t struggle with.”

**MITIGATING CHALLENGES ASSOCIATED WITH G-CSF TREATMENTS**

Although treatment with G-CSFs is generally well tolerated, they are associated with several toxicities, including bone pain. Rugo explained that bone pain is more common in patients with naïve bone marrow but that some patients “seem to get it all the time.” In patients with bone pain, an important step is for clinicians to determine its cause, including whether it is related to the patient’s chemotherapy regimen or to the growth factor support, especially because bone pain can be mistaken for a myocardial infarction or other complications and lead to unnecessary hospitalizations and procedures.

“I have a patient who has von Recklinghausen neurofibromatosis and a bunch of other things, including...ER [estrogen receptor]-positive early-stage breast cancer,” Rugo said. “She has had severe bone pain and went to the emergency department, where [she received a diagnosis of] pericarditis. I pointed out that she didn’t have that, but they didn’t believe me—she just had this drug-induced pain. Consequently, we’re working around that, but it can be a big issue for patients.”

Once it is determined that the bone pain is induced by the growth factor support, Gradishar said he will treat his patients with a course of steroids or antihistamines, as these can be helpful in resolving the pain in some cases. Rugo agreed and said that she usually prescribes non-narcotic antihistamines. Although they work variably, and the mechanisms by which they improve bone pain remains unclear, she said these agents have “little downside” because they are “cheap and nontoxic.”

Because bone pain from G-CSFs usually occurs quickly after their administration, Nanda said that she forewarns her patients.”

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—RITA NANDA, MD
about this complication and advises them to take over-the-counter (OTC) anti-inflammatory medications if they notice any pain. Then, if the OTC treatment does not work, they are advised to call the office so that they can be prescribed steroids.

Another challenge the panelists discussed is delivery of G-CSF via an on-body device. Although these devices spare patients from returning to their doctor’s office the day after their infusion, they come with other restrictions. Traina noted that patients with such devices can’t have imaging done, which may lead to other care challenges and make it difficult to travel if they need to fly. Additionally, the on-body devices do not provide flexibility in dosing and there may be drug delivery issues in some patients.

“Clinicians would often give different amounts of pegfilgrastim if [patients] didn’t need the full dose, but with the on-body device, we can’t do that,” Rugo said. “Additionally, I’ve had a very overweight patient for whom I don’t think the drug was delivered. She kept getting profound neutropenia, and then as soon as we switched to the injection, on day 2 it went away.”

REFERENCES
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