Immunotherpay • Biomarkers • Pathways

ESMO I-O

Triplett Achieves High Disease Control in R/M SCCHN

The addition of the anti-NKG2A antibody monalizumab (formerly IPH2201) to cetuximab and durvalumab (Imfinzi) showed significant disease control in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), according to findings from a cohort of the phase 1/2 IPH2201-203 trial (NCT02643550). Results presented during the European Society for Medical Oncology Immuno-Oncology Congress 2021 demonstrated that 35 of 40 participants achieved a response rate of 87.5% in the cohort.

“These data support the statement that monalizumab, cetuximab, and durvalumab show promising activity in these patients with recurrent squamous cell carcinoma of the head and neck, [and it’s particularly noteworthy that this is] a chemotherapy-free regimen with a very low AE [adverse event] profile,” said A. Dimitrios Colevas, MD, professor of medicine, otolaryngology, and radiation oncology at Stanford Cancer Center, and member of Stanford Cancer Institute in California. Monalizumab is a first-in-class checkpoint inhibitor targeting the CD94/NKG2A receptor. NKG2A is expressed on subsets of natural killer cells and tumor-infiltrating CD8-positive T cells, and inhibiting leads to innate immunity and

SPECIAL REPORT

Seeking Clarity for Treatment Sequencing With CAR T in Follicular Lymphoma

Biomarkers Improve Targeting and Risk Assessment in Endometrial Cancer

Biomarkers such as mismatch repair deficiency (dMMR), microsatellite instability (MSI), p53 positivity, and POLE mutations can inform treatment and care options in patients with endometrial cancer, but the search to deliver optimal care continues. To reach that goal, patients can be stratified by risk, traditional staging

ASCO PLENARIES

Findings From INTRIGUE Keep Ripretinib in the Advanced GIST Landscape

Based on the median progression-free survival (PFS) observed with ripretinib (Qinlock) in the phase 3 INTRIGUE trial (NCT03673501), the agent may provide clinical benefit to patients with advanced gastrointestinal stromal tumor (GIST), despite the PFS not being superior to sunitinib malate (Sutent) and missing the primary end point of the study. Results presented during the January American Society of Clinical Oncology (ASCO) Plenary Series showed that ripretinib did perform better than sunitinib in terms of the objective response rate (ORR) and that its safety profile was favorable compared with sunitinib.

PER® SPOTLIGHT: GI CANCERS

Exploring the Emerging Role of Circulating Tumor DNA in Colorectal Cancer

This year’s plenary session at the 7th Annual School of Gastrointestinal Oncology® (SOGO®) is tackling the emerging role of circulating tumor DNA (ctDNA) in colorectal cancer (CRC). The presentation will be delivered by conference co-chair Michael A. Choti, MD, who is chief of

Challenges for MET Inhibitors in NSCLC

Martin Dietrich, MD, PhD, University of Central Florida, discusses guidelines for MET inhibitors in patients with non–small cell lung cancer. View at: targetedonc.com/link/1606
INDICATION 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).

IMPORTANT SAFETY INFORMATION
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 serious or severe 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 maculo-papular), and erythema.
Cutaneous Reactions (continued)
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 embryo-fetal 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.

ADVERSE REACTIONS
In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.
In LOTIS-2, 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.
Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.
Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.
Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

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.

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

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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 143 patients from LOTIS-2 treated with 0.15 mg/kg × 2 cycles followed by 0.375 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, hypoalbuminemia, 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.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

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><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></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><strong>Gastrointestinal Disorders</strong></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><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>23</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>10</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
</tr>
</tbody>
</table>

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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) All Grades (%)</th>
<th>Grades 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>1a</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
<td>3a</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>30</td>
<td>2a</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
<td>2a</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>2a</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
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<tr>
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<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>57</td>
<td>21</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>AST increased</td>
<td>41</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ALT increased</td>
<td>34</td>
<td>3</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value.

**No Grade 4 adverse reactions occurred

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 to loncastuximab tesirine-Ipyl in other studies or to other products may be misleading.

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine-Ipyl after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal 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 2.2% and 15% respectively.

**Data**

**Animal Data**

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine-Ipyl. The cytotoxic component of ZYNLONTA, SG3199, crosslinks 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-Ipyl 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 6 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 > 1.5 × 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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Follicular lymphoma is different from DLBCL... in that most of these patients have an indolent disease, and a relapse in follicular lymphoma does not mean you have to treat the patient right away.” JOSE ANDOVAL-SUS, MD PAGE 22

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47 Exploring the Emerging Role of Circulating Tumor DNA in Colorectal Cancer
Search for Emerging Biomarkers Continues in Solid Tumors and Hematologic Malignancies

Emerging biomarkers continue to be a primary objective in research efforts across cancer settings. Given the heterogeneous biology of the disease, biomarkers and subsequent druggable targets represent potential areas of improvement for patient care. In this issue of Targeted Therapies in Oncology™, we look at the biomarker field in endometrial cancer and multiple myeloma.

In an interview with Targeted Therapies in Oncology™, Casey M. Cosgrove, MD, of The Ohio State University College of Medicine, touched on his presentation during the Society of Gynecologic Oncology 2022 Winter Meeting (page 42). In particular, Cosgrove discussed the RAINBO trial, an international study that seeks to improve the management of endometrial cancer by approaching the cure from a molecular-driven strategy. After surgery, patients with endometrial cancer will be recruited to 4 independent and parallel trials based on molecular profiling: p53 abnormality, mismatch repair deficiency (MMRd), POLE mutation, and no specific molecular profile (NSMP).

The p53 abnormality trial will evaluate maintenance therapy with niraparib (Zejula) after chemoradiotherapy; MMRd trial will investigate adjuvant PD-L1 inhibitors; NSMP trial will compare chemoradiotherapy vs radiation therapy plus hormonal therapy; and the POLE-mutant trial is an observation study for patients with all stages of POLE-mutant endometrial cancer.

The search for biomarkers continues in multiple myeloma where the goal of personalizing patient treatment can lead to improved outcomes. Multiple myeloma, with its complex etiology, demonstrates the need to expand the established field of biomarkers, which remains an important objective in research. In this issue’s Precision Medicine in Oncology® column (page 49), biomarkers such as minimal residual disease, translocation (11;14), circulating tumor cells, and microRNAs are explored.

In an interview for the article, Mark Bustoros, MD, of Weill Cornell Medicine, noted the potential of biomarkers such as deletion 17p and gain 1q might provide insight into resistance mechanisms. The presence of these genetic alterations may signal poor outcomes for these patients. In another interview, Thomas G. Martin, MD, of the University of California, San Francisco, noted the potential of serum B-cell maturation antigen (BCMA) levels. Current trials suggest patients with higher baseline serum BCMA levels had poorer progression-free and overall survival outcomes.

Across cancer settings, the role of biomarkers continues to expand. With each advance, personalized medicine becomes a reality for every patient with cancer. We will continue sharing these developments in the pages of Targeted Therapies in Oncology™.

Mike Hennessy Jr
President & CEO
Lukewarm Outcomes for Durvalumab in HNSCC Don’t Deter Triplet IO Combinations

WE CONTINUE TO observe the steady pace of drug development, which employs rational combinations based on preclinical science and biology paired with promising small development trials. Fortunately, innovative agents are still able to emerge, allowing for progress through further clinical evaluation even when early trial results are equivocal.

From the European Society for Medical Oncology (ESMO) Immuno-Oncology (IO) Congress 2021, 1 particular trial deserves mention as an exemplar. In head and neck squamous cell carcinoma (HNSCC) there has been a drought of recent positive trial data. Although further IO combinations with doublet immune checkpoint inhibitor combinations continue to be tested, a different strategy targeting natural killer (NK) cells has shown promise.

Findings from the phase 1/2 clinical trial IPH2201-203 (NCT02643550) showed a confirmed objective response rate (ORR) of 32.5% for all patients, regardless of PD-L1 status, and the unconfirmed ORR was 50% [page 31]. This result compares favorably with the CheckMate 651 trial (NCT02741570) or pembrolizumab (Keytruda) plus chemotherapy in the KEYNOTE-048 trial (NCT02358031). The combined positive score of PD-L1 greater than 1 was 63% vs 80% in other trials, so this was not necessarily a cohort that was highly immune responsive. A combination of cetuximab (Erbitux) and monalizumab that blocks an inhibitory receptor in NKG2A on NK cells had previously shown activity in recurrent or metastatic HNSCC and in a separate cohort of patients who were PD-1 refractory. Given these exciting early data, the cetuximab and monalizumab combination appears to be enhanced with the addition of durvalumab (Imfinzi). Indeed, durvalumab is not approved for HNSCC despite indications of its activity in first- and second-line trials that were negative overall. Durvalumab had “failed” in prior HNSCC phase 3 trials, though a glimmer of activity was observed. This example of developing new immunobiology translating to the clinic is innovative because it does not simply rely on a new T-cell targeted immunotherapy but rather on harnessed NK cells, long felt to be key antitumor immune effectors and helper cell.

Butressed by the promising data from those trials of development of activity in HNSCC, AstraZeneca saw enough activity to remain enthusiastic about prospects for durvalumab, used here as a triplet IO regimen. This is a model for the field to progress multiple antibody combinations and possibly re-introduce specific agents which had not succeeded alone in other trials but may leverage other target assets using rational biological combinations.
The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

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

Consistent results with or without prior adjuvant chemotherapy2‡

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

*Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.¹

¹Control arm=placebo.

Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.16 (95% CI: 0.10, 0.26) and for patients without adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).²

CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

INDICATION

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

SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO

- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

TAGRISSO is a registered trademark of the AstraZeneca group of companies. ©2021 AstraZeneca. All rights reserved. US-53566 5/21
† Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.1

• Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is suspected, consider permanent discontinuation of TAGRISSO based on severity.

• Veriﬁcation of EGFR status in every surgical specimen for EGFR mutations is recommended, and every resected NSCLC patient should be referred to a medical oncologist for adjuvant therapy if eligible. Investigators should verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose.

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

and fever). Permanently discontinue TAGRISSO if ILD is confirmed [see Dosage and Pharmacology (12.3) in the full Prescribing Information].

Prior to treatment with TAGRISSO and for up to 3 years.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

In patients with metastatic lung cancer during progression or unacceptable toxicity.

If adnexal structure is tumor is present, tag the patient as non-compliant and do not provide further treatment.

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed for up to 3 minutes. If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Select patients for the treatment of metastatic EGFR T790M mutation-positive NSCLC with permanent discontinuation of TAGRISSO based on the presence of EGFR T790M mutation in tumor or plasma specimens. If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

The recommended dosage of TAGRISSO is 80 mg tablet once a day. TAGRISSO can be taken with or without food.

Use in Specific Populations (8.1, 8.3) in the full Prescribing Information.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 555 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive NSCLC who had not received prior systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months. Clinical trials of TAGRISSO did not enroll patients with baseline QTc of >470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, as these patients are at risk for a prolonged QTc interval which may result in the occurrence of ventricular arrhythmias or sudden death.

The most common serious adverse reaction (>1%) was pneumonitis (3.2%). The most frequent adverse reactions leading to dose reductions or interruptions were diarrhea (9.3%), vomiting (9.3%), and rash (9.3%). Adverse reactions leading to permanent discontinuation occurred in 11% of patients treated with TAGRISSO. The most frequent adverse reactions leading to discontinuation of TAGRISSO were interstitial lung disease (2.2%), and rash (1.2%).

Table 2. Adverse Reactions Occurring in >25% of Patients Receiving TAGRISSO in ADJUVAN®

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=387)</th>
<th>PLACERO (N=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>3.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.4</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Table 1. Recommended Dosage Modification for TARGRISO

<table>
<thead>
<tr>
<th>Organs</th>
<th>Adverse Reaction</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>QTc interval &gt; 450 msec or &gt;2 equal ECGs</td>
<td>Tag to TAGRISSO until QTc interval is less than 450 msec or recovery to baseline if baseline QTc is greater than or equal to 461 msec; then resume at 40 mg dose</td>
</tr>
<tr>
<td>Heart</td>
<td>QTc interval &gt; 450 msec or &gt;2 equal ECGs</td>
<td>Tag to TAGRISSO until QTc interval is less than 450 msec or recovery to baseline if baseline QTc is greater than or equal to 461 msec; then resume at 40 mg dose</td>
</tr>
</tbody>
</table>

Table 3. Laboratory Abnormalities Worsening from Baseline in <2% of Patients in ADJUVAN®

<table>
<thead>
<tr>
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<th>TAGRISSO (N=387)</th>
<th>PLACERO (N=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Neutropenia</td>
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</tr>
<tr>
<td>Anemia</td>
<td>13.4</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Table 4. Summary of common adverse reactions and laboratory abnormalities which occurred in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>6.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Table 5. Summary of common adverse reactions and laboratory abnormalities which occurred in FLAURA
Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 29% in the chemotherapy group when single-agent adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (LD/premature death).

Dose reductions occurred in 29% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.1%), hyperglycemia (1.1%), and diarrhea (1.1%). Adverse reactions reported in 10% or more patients treated with TAGRISSO were:

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>58</td>
<td>52 (N=26)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>12 (N=12)</td>
</tr>
<tr>
<td>Transaminases (ALT)</td>
<td>14</td>
<td>13 (N=13)</td>
</tr>
<tr>
<td>Lipase</td>
<td>11</td>
<td>11 (N=11)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>2</td>
<td>1 (N=1)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1</td>
<td>1 (N=1)</td>
</tr>
</tbody>
</table>

The most frequent adverse reactions leading to treatment discontinuation (≥1% or at least twofold increase in any laboratory abnormality from baseline) were:

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THE POWER OF COMMUNITY

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The FDA has granted approval to tebentafusp-teb ($\text{Kimmtrak}$) for the treatment of patients who are HLA-A*02:01-positive and who have unresectable or metastatic uveal melanoma, according to a press release from Immunocore Holdings plc. The approval is supported by data from the phase 2 IMCoG0100-202 (NCT03070392) clinical trial, in which tebentafusp led to prolonged overall survival (OS) in patients with previously untreated metastatic uveal melanoma compared with the investigator’s choice of dacarbazine, ipilimumab (Yervoy), or pembrolizumab (Keytruda).

“Uveal melanoma is a devastating disease that has historically resulted in death within a year of metastasis,” said John Kirkwood, MD, director of the Melanoma Center at the UPMC Hillman Cancer Center, in a press release. “The approval of Kimmtrak represents a major paradigm shift in the treatment of metastatic uveal melanoma and, for the first time, offers hope to those with this aggressive form of cancer.”

In the randomized, open-label, multicenter IMCoG0100-202 study, 378 patients with metastatic uveal melanoma who were at least 18 years of age with histologically or cytologically confirmed disease, HLA-A*02:01-positive by central assay, had a life expectancy of at least 3 months, an ECOG performance status of 0 or 1, and measurable disease per RECIST v1.1 were included. The study population was evaluated for the primary end point of OS and multiple secondary end points, including the number of patients with adverse events (AEs), progression-free survival (PFS), quality of life, pharmacokinetics, objective response rate, duration of response, and disease control rate.

The hazard ratio for OS with tebentafusp compared with the investigator’s choice of therapy was 0.51 (95% CI, 0.37-0.71; P < .0001). At 1 year, the OS rate with tebentafusp was 73% compared with 59% in the control group. The 6-month PFS rate was also longer in patients treated with tebentafusp at 31% compared with 19% in the investigator’s choice arm (HR, 0.73; 95% CI, 0.58%-0.94%; P = .01).

The most common treatment-related AEs (TRAEs) with tebentafusp were cytokine-mediated events caused by T-cell activation and skin-related events caused by glycoprotein 100–positive melanocytes. The TRAEs specifically included rash (38%), pyrexia (7%), and pruritus (69%). Notably, the incidence of TRAEs decreased over time. Regarding grade 3 and 4 TRAEs, severity did lead to treatment discontinuation in 2% of patients. There were no treatment-related deaths reported in the study.

The FDA approval for tebentafusp follows a breakthrough therapy designation for unresectable or metastatic uveal melanoma and aligns with a Prescription Drug User Fee Act target action date assigned to the biologics license application, which was granted priority review by the FDA in August 2021.

FAM-TRASTUZUMAB DERUXTECAN-NXKX (ENHERTU)

A supplement biologics license application for fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) has been granted priority review by the FDA. The agent is indicated for the treatment of adult patients with unresectable or HER2-positive metastatic breast cancer (mBC) who have received a prior anti–HER2-based regimen, according to a press release from Daichi Sankyo Company, Limited.

In the phase 3, multicenter, randomized, open-label, active-controlled DESTINY-Breast03 study (NCT03529110), a highly statistically significant and clinically meaningful improvement in progression-free survival (PFS) was shown with T-DXd vs ado-trastuzumab emtansine (T-DM1, Kadcyla) in patients with HER2-positive mBC who were previously treated with trastuzumab (Herceptin) and a taxane.

The study randomized 524 patients 1:1 to receive either T-DXd or T-DM1. The primary end point of the study was PFS by blinded independent central review (BIRC). The secondary end points included overall survival (OS), objective response rate (ORR), duration of response, PFS by investigator assessment, and safety. According to investigator assessment, the median PFS was 14.3 months (range, 0.7-29.8) with T-DXd and 6.9 months (range, 0.7-25.1) with T-DM1. Treatment-emergent adverse events were observed in 98.1% of the T-DXd arm vs 86.6% of the T-DM1 arm. Events were grade 3 or higher for 45.1% of the experimental arm vs 39.8% of the control arm. Treatment discontinuation related to a study drug occurred in 12.8% of the T-DXd arm vs 5.0% of the T-DM1 arm, and dose reductions occurred in 21.4% vs 12.6%, respectively.

The FDA has accepted a supplemental biologics license application (sBLA) for cemiplimab-rwlc (Libtayo) in combination with chemotherapy as first-line treatment in advanced non–small cell lung cancer (NSCLC), according to a press release by Regeneron Pharmaceuticals, Inc. The application will undergo a traditional review by the FDA, and the target action date for the FDA’s decision has been set for September 19, 2022.

Results from the randomized, multicenter phase 3 EMPOWER-Lung 3 (NCT03086540) trial of frontline cemiplimab and platinum-based chemotherapy support the sBLA. In the study, patients treated with cemiplimab/chemotherapy showed an improvement in overall survival (OS) compared with patients who received chemotherapy alone.

In 466 patients, cemiplimab in combination with chemotherapy reduced the risk of death by 29% compared with chemotherapy alone in the study subjects (HR, 0.71; 95% CI, 0.53%-0.93%; P = .014). The median OS observed with cemiplimab was 22 months (95% CI, 16- not evaluable) vs 13 months (95% CI, 12-16) with chemotherapy. The study was stopped early due to the positive OS result.

No new safety signals were observed. Treatment discontinuation occurred in 5% of the cemiplimab and chemotherapy arm compared with 3% of the chemotherapy-alone arm. Immune-mediated adverse events were reported in 19% of the experimental arm.
**GEDATOLISIB | JANUARY 18, 2022**

The FDA has granted a fast track designation to gedatolisib for the treatment of patients with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (mBC) after progression on CDK4/6 therapy, announced Celularity Inc, in a press release. Gedatolisib, a potent, reversible dual PI3 kinase (PI3K) and mTOR inhibitor, has been shown preclinically to limit the potential development of drug resistance compared with similar isoform-specific PI3K inhibitors. Gedatolisib also achieved a robust response rate and was well tolerated with manageable toxicity in a phase 1b study.

In the ongoing multicenter, open label, phase 1b B2151009 study (NCT02684032), gedatolisib has been administered in combination with either palbociclib (Ibrance) and letrozole (Femara) or palbociclib and fulvestrant (Faslodex) to women with mBC. Approximately 141 patients have been enrolled and assigned to receive gedatolisib 180 mg per week in a 4-week cycle in combination with palbociclib 125 mg daily given for 3 of 4 weeks in a 4-week cycle, and letrozole 2.5 mg daily in 1 experimental arm or the same doses of gedatolisib and palbociclib with fulvestrant administered intramuscularly at 500 mg on day 1, 15, and 28, and then every 28 days. The study arms also include 2 dose-escalation and 2 dose-expansion arms. In 88 evaluable patients, the overall response rate was 60% with a 75% clinical benefit rate.

Treatment with gedatolisib appeared to be well tolerated during the study with most treatment-related adverse events (TRAEs) being grade 1 or 2. The most common grade 3 or 4 TRAEs observed were stomatitis and rash. Ten percent of patients in the study discontinued gedatolisib.

**CYNK-101 | JANUARY 18, 2022**

CYNK-101 with standard frontline chemotherapy, trastuzumab (Herceptin), and pembrolizumab (Keytruda), has been granted a fast track designation by the FDA for the treatment of patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma, according to Celularity Inc, the developer of the genetically modified natural killer (NK) cell therapy.

A phase 1/2a study is currently being planned to test the safety and preliminary efficacy of the combination. This study will assess the addition of CYNK-101 to the triplet combination offers direct NK cell tumor killing, and helps with T-cell function limit resistance.

**C-CAR039 | JANUARY 12, 2022**

The FDA has granted both a fast track designation and a regenerative medicine advanced therapy designation to the autologous bispecific CAR T-cell therapy that targets both CD19 and CD20, C-CAR039, for the treatment of relapsed or refractory (R/R) diffuse large B-cell lymphoma, according to a press release by Cellular Biomedicine Group Inc (CBMG). The agent was previously granted clearance for clinical development by the FDA for the treatment of patients with R/R non-Hodgkin lymphoma (NHL).

The clearance granted phase 1b clinical development of the agent. C-CAR039 has also been granted an orphan drug designation for the treatment of follicular lymphoma. A study of the agent conducted in China found that it had a promising efficacy and safety profile.

As of April 2021, 34 patients had received C-CAR039, with 28 patients being evaluable for safety and 27 for efficacy. The best overall response rate was reported at 92.6%, with a complete response of 85.2%. The median time to response was 1 month. At a median follow-up of 7 months, 74.1% remained in complete remission. The estimated 6-month progression-free survival was at 83.2% (95% CI, 69.1%-100.0%).

In terms of safety, 94% experienced cytokine release syndrome, with 92% of cases being grade 1 or 2. Only 1 patient experienced grade 3 cytokine release syndrome. All immune-effector cell-associated neurotoxicity syndromes were grades 1 or 2. No grade 3 or higher neurological events were reported. Longer follow-up studies of C-CAR039 are currently planned.

**ENOBOSARM (MK-2866) | JANUARY 10, 2022**

The FDA has granted a fast track designation to enobosarm (MK-2866) for the treatment of patients with androgen receptor (AR)-positive, estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer (mBC) who have shown previous disease progression on a nonsteroidal aromatase inhibitor, fulvestrant (Faslodex), and CDK4/6 inhibitor therapy, and who have AR nuclei staining of at least 40% in breast cancer tissue, according to a press release by Veru Inc.

Enobosarm, a selective AR-targeting agonist, is under investigation as monotherapy, in the phase 3, multicenter, randomized, open-label ARTEST trial (NCT04869943). The study's primary end point is progression-free survival, and the secondary end point is overall response rate.

ARTEST is ongoing at 50 study locations throughout the United States, as well as in Poland, Spain, and Ukraine. A phase 3 study of enobosarm in combination with abemaciclib (Verzenio) is also underway (ENABLAR-2; NCT05065411) to evaluate the efficacy and safety of the combination in patients with AR-positive, ER-positive, HER2-negative mBC, whose disease is resistant to palbociclib, an estrogen-blocking agent.
HERE IS STILL plenty of time to set financial goals for 2022. Keeping track of goals and checking them throughout the year will build on successes month by month.

Make asset protection a priority
According to the American Medical Association (AMA), 60% of physicians over the age of 50 years will be involved in a lawsuit at least once. This statistic is even higher for specific types of physicians such as OB-GYNs and surgeons. It’s important to speak to an attorney and discuss various asset protection strategies such as Nevada Asset Protection Trusts, limited liability companies, or family limited partnerships to make sure your assets are protected from frivolous lawsuits.

Prepare your will and trusts
Estate planning, including a properly drafted will and trusts, allows for peace of mind with the knowledge that your estate will be distributed exactly as you wish and that your family will be cared for. Do not wait to prepare these documents.

Take advantage of employer-sponsored plans
If you are a hospital-based physician, enroll in and contribute the maximum to employer-sponsored retirement savings plans. Depending on the options available, there may be extra advantages such as employer match contributions and automatic deductions. Take the time to learn the details of the plan to take advantage of any tax benefits and retirement savings.

Max out your own accounts
If you are a self-employed physician, personal retirement accounts are another good way to save, with the annual maximum individual retirement account (IRA) contribution currently at $6000. For those who are older than 50 years, the catch-up amount is $1000 for a total of $7000. A backdoor Roth IRA may also be an option, particularly for those who have maxed out their 401k plans. To get the tax-free growth and tax-free withdrawal benefits of a Roth IRA, after-tax dollars contributed to an IRA can be converted to a backdoor Roth IRA. Self-employed physicians should also speak to their certified public accountant about contributing to a simplified employee pension (SEP) IRA and a cash balance plan for their practice.

Set a budget
Sticking to a budget is the first step to keeping financial goals in sight.

Don’t wait to start saving
The earlier you start your retirement savings, the more you will benefit from compounding.

Lower credit card and student debt
Credit card debt adds up quickly and the high interest rates can whittle away at potential savings. Pay off those debts as quickly as possible and use budgeting tools to spend within your means going forward.

Diversify your investments
Contributing to your retirement accounts is one step; the next is diversifying, which provides some protection to investments.

Become informed about Social Security and Medicare
Social Security helps most people, regardless of investment planning. Waiting to claim those benefits will earn you delayed credits that will increase your benefits annually until age 70, resulting in a larger benefit to you and your family. Be ready to sign up with Medicare as soon as you are eligible at age 65 and make sure you understand the plans you sign up for. Medicare Part B concerns medical insurance, and you can choose from among various plans to find the one that works best for you.

Keep an eye on your health and stress level
Your health is part of your financial planning. Look outside of work for other interests and take time to pursue new skills and hobbies, travel, and volunteer work in your community.

These steps may seem overwhelming. Because of the complicated nature of financial planning, you may benefit from working with an experienced financial advisor.

For further information, visit: https://bit.ly/3G5ijvQ
**Differentiating Pseudoprogression From Hyperprogression in Patients Treated With Immunotherapies**

By Kashyap Patel, MD; Hirangi Mukhi, BS; Anjana Patel, BSc; Dhwani Mehta, MS, Natasha Clinton, MSN, APRN, AOCNPS; Ben Brown; Sara Rogers, PharmD, BCPS; William Oh, MD; Prasanth Reddy, MD, MPH

**The Rapid Progression of Novel Immune-Based Treatment Strategies in Solid Tumors—Beginning with the Approval of Immune Checkpoint Inhibitors (ICIs) for Melanoma in 2011 and Subsequent Approval of Numerous Agents in the ICI Therapeutic Category—Has Revolutionized Treatment of Advanced Cancers That Were Deemed Invariably Fatal Until the Past Decade.**

Faster development of novel biomarker-driven targeted therapies has accelerated hope and optimism about converting advanced solid tumors into chronic diseases. These advances have also led to the recognition of other clinical challenges, including unforeseen observations and complications associated with choosing the sequencing of appropriate therapeutic interventions as well as the management of drug-related complications. One critical enigma facing clinicians is how to differentiate between pseudoprogression (PSP), true disease progression (TDP), and hyperprogression (HPD). These phenomena are observed in patients treated with ICIs targeting CTLA-4, PD-1, or PD-L1 that are approved for use across multiple types of advanced cancers. The lack of consensus or an analytic framework to decipher between early indications of PSP, TDP, and HPD may expose patients to avoidable harm.

Another challenge centers around selecting the most appropriate therapeutic intervention when broad-based genomic profiling results reveal multiple actionable biomarkers vs actionable genomic driver mutations such as those found in EGFR, ALK, ROS1, and a number of other targetable pathogenic genomic alterations. Selecting the right drug at the right time for patients is further complicated by these considerations:

- The disparate timing of receiving results from PD-1/PD-L1 immunohistochemistry testing vs next-generation sequencing (NGS) testing
- Determining the adequacy of NGS panel testing with negative results, whether using a whole exome sequencing or comprehensive genomic profiling approach

**Clarifying PSP, TDP, and HPD**

For this review we will confine our discussion to the clinical impact associated with the determination of PSP, TDP, and HPD following ICI therapy. Even the definitions of TDP, PSP, and HPD have not reached uniform consensus, so we will focus on clinical implications.

Although an accurate consensus has not been reached on defining PSP or HPD, differentiating between those clinical states is critically important. PSP indicates efficacy of ICI therapy, whereas HPD portrays ineffective treatment with ICIs resulting in a rapid negative clinical outcome in most cases. PSP is a type of response to ICI therapy accompanied by an apparent initial increase in tumor size or new lesions, which potentially appear upon radiological assessment, followed by an eventual decrease in tumor burden. Although this response favors patients receiving ICI therapy, a lack of awareness can lead to premature discontinuation of treatment because of an incorrect clinical interpretation of disease progression.

The incidence of ICI therapy-associated PSP varies from 3.70% to 15% in different tumor types. PSP is a relatively uncommon response defined as an initial increase of tumor size followed by a measurable response to treatment. ICI therapy-associated PSP results from an exacerbated immune cell infiltration in the tumor bed (T cells expressing CD103+ and CD8+). Another postulated mechanism of PSP described by Cohen et al occurred in a case of PSP involving brain metastases in a patient with melanoma after treatment with pembrolizumab (Keytruda). The histology revealed an inflammatory reaction identified as isolated clusters of tumor cells surrounded by reactive astrocytosis and inflammatory cells. PSP associated with ICI therapy carried a higher likelihood of 1-year survival when compared with TPD. Failure to distinguish PSP from TPD may result in premature discontinuation of treatment with ICI, leading to adverse outcomes. It is crucial to distinguish between TPD and PSP.

HPD can be defined as an accelerated tumor growth pattern after exposure to ICI therapy, with an increase in the absolute mass of tumor cells in a relatively short...
time. Possible explanations of HPD in response to ICI may include the expansion of PD-1-positive regulatory T cells, exhaustion of compensatory T cells, modulation of protumorigenic immune cell subsets, and activation of aberrant inflammation cell cycle signaling.\(^1\) HPD may be observed as a rapid escalation in the size and bulk of masses of measurable tumor volume, the appearance of numerous new lesions, and/or rapid deterioration in organ function leading to symptomatic disease progression (similar to jaundice from a rise in bilirubin and liver enzymes), and/or shortness of breath from the progression of metastases in the lungs or deterioration of brain metastases leading to worsening central nervous system symptoms. Efforts have been made to define HPD based on tumor growth rate (TGR), tumor growth kinetics (TGK), and other RECIST parameters to better define HPD. However, such efforts are often in isolation and limited to institution-based criteria.

Park et al\(^{14}\) published a study after exhaustive and systematic analysis to define HPD. They concluded that the clinical interpretation of HPD appears diverse, with the incidence of HPD varying from 5.9% to 43.1% across studies examined in their meta-analysis. They also highlighted the critical unmet need for establishing uniform and clinically relevant criteria based on currently available evidence to define HPD. One of the most compelling reasons to identify true HPD is the association of patients with HPD with extremely poor prognosis. Several studies reported worse progression-free survival and overall survival in the subgroup analysis of patients with HPD.\(^{5,15}\) Earlier identification of patients with HPD could lead to quicker adjustment of therapeutic selection to improve the dismal clinical outcomes currently associated with HPD. Because there remains no clear consensus around the definition of HPD at the time of writing this article, we simply define HPD as resulting in the rapid clinical acceleration of tumor growth resulting in shortened patient survival.

**New Clinical Challenges**

With the rapid strides in immune-based treatment options in patients with advanced solid tumors in the past decade, we have seen significant clinical improvement in patient quality of life and quantitative improvement of clinical outcomes. However, increased utilization of ICI therapies has also led to the recognition of new clinical challenges associated with a small but not insignificant number of patients, where failure to distinguish between TPD, PSP, and HPD clearly has an impact on patient lives. It is critical that our research communities start paying more attention to and providing clinical guidance around the following issues:

- **Recognition of HPD as a clinical phenomenon and not just a concept characterized by acceleration of measurable and quantifiable disease by radiologic assessment**
- **With the reported incidence of HPD being higher compared with PSP, emphasizing the importance of identifying HPD as early as possible, because it can occur within weeks of starting ICI therapy and result in higher mortality**
- **Establish clear criteria that may facilitate and support conclusive assessment of HPD vs either true PD or PSP, which may include assessment of TGR, TGK, number and increase in metastatic lesions, growth in size of the target lesions, and additional RECIST-defined criteria**
- **Create a consensus of baseline timing of imaging studies prior to starting ICI treatment as it can impact interpretation of subsequent studies either as a standard of care or symptom directed protocols to make it easier to correlate to pretreatment findings to distinguish between TPD, PSP, and HPD**
- **Continue research to establish whether HPD is related to specific cancer subtypes or other patient comorbidities, including preexisting conditions**
- **Identify whether HPD is therapeutic agent specific or class specific (ie, anti-CTLA, anti-PD-1, or anti-PD-L1 therapies)**

Although ICI approaches are now a mainstay in therapy, challenges to optimal benefit, such as PSP, TDP, and HPD, require continued vigilance. TT

**REFERENCES**

Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 5% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA® [see Use in Specific Populations (8.1, 8.3)].

ADVERSE REACTIONS

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≤2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decrease, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)

• Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 7% (0.4%), placebo 6% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)

• Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59%
ERLEADA® (apalutamide) is an androgen receptor inhibitor. In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and 2% of patients treated with placebo. In TITAN, 0.4% of patients treated with ERLEADA® and 0.2% of patients treated with placebo died from a cerebrovascular event.

**Hypothyroidism** — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 1.5% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

### DRUG INTERACTIONS

**Effect of Other Drugs on ERLEADA®**

Co-administration of a strong CYP3A4 or CYP2C9 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (see Dosage and Administration (2.2)).

**Effect of ERLEADA® on Other Drugs**

CYP3A4, CYP2C9, and UGT Substrates — ERLEADA® is a strong inducer of CYP3A4 and CYP2C9, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C9, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity. P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

**References:**


**Visit erleadahcp.com**

**References:**

1. TITAN = Targeted Investigational Treatment Analysis of Novel Androgens.
2. Study Design: TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=11,052). Patients had newly diagnosed mCSPC or prolonged metastatic disease after an initial diagnosis of localized disease. Patients with visceral (ie, liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchectomy. The dual primary endpoints were overall survival and rPFS.1
3. Patients who enrolled in the TITAN study started ADT for mCSPC ≤6 months prior to randomization.
4. Study Design: SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=1,270). Patients had a PSA doubling time ≤10 months, and serum testosterone levels ≤50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review.
5. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a bilateral orchectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the first time of evidence of blinded independent central review-confirmed distant metastases, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastatic, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.1
6. In the SPARTAN study, conventional imaging (technetium-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph nodes ≤2 cm in short axis (N1) located below the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastatic, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.1
7. In the SPARTAN study, conventional imaging (technetium-99m bone scans and CT scans) was used to confirm that patients were non-metastatic at screening for inclusion. Patients with pelvic lymph nodes ≤2 cm in short axis (N1) located below the iliac bifurcation at screening were allowed in the study. All patients in SPARTAN had a PSA doubling time ≤10 months at study entry.1
ERLEADA® (apalutamide) tablets

Ten patients (1.9%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), suicide (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2.3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (n=3) were fatigue, rash, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in >10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently ≥35% in the ERLEADA arm compared to placebo.

### Table 1: Adverse Reactions in TITAN (mCrPC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>26 (5.0%)</td>
<td>9 (1.7%)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>16 (3.0%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (1.3%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (2.1%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>9 (1.7%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>5 (0.9%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>3 (0.6%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Rash exfoliative</td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (1.5%)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (0.9%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (0.6%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (0.6%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

### Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference ≥ 5%) in TITAN (mCrPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27 (5.1%)</td>
<td>19 (3.6%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>17 (3.2%)</td>
<td>12 (2.3%)</td>
</tr>
</tbody>
</table>

### WARNINGS AND PRECAUTIONS

**Cerebrovascular and Ischemic Cardiovascular Events**

Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients treated with ERLEADA. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with mCrPC, ischemic cardiovascular events occurred in 3.7% of patients treated with ERLEADA and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with asymptomatic mCrPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA and 1% of patients treated with placebo [see Adverse Reactions]. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from cerebrovascular disorders.

### Fractures

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 2.7% of patients treated with ERLEADA and in 0.8% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 203 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 1.5%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

### Fails

Fails occurred in patients receiving ERLEADA with increased frequency in the elderly [see Use in Specific Populations]. Evaluate patients for falls risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

### Seizure

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 680 days after treatment with ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

### Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥2 times the human clinical exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA [see Use in Specific Populations and Clinical Pharmacology (12.1) in Full Prescribing Information].

### ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

### Clinical Trial Experience

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

The most common adverse reactions that occurred more frequently in the ERLEADA-treated patients (> 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, flat, weight decreased, hypertension, headache, and fracture.

### Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. Patients were treated until progression, discontinuation at the investigator’s discretion, or when patients withdrew consent. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0 to 34 months) in patients who received placebo.
ERLEADA® (apalutamide) tablets

\[ \text{\textsuperscript{4}} \text{ Includes appetite disorder, decreased appetite, early satiety, and hypophagia} \]
\[ \text{\textsuperscript{1}} \text{ Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema} \]

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (8% versus 1.5% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and a Higher Incidence than Placebo (Between Arm Difference ≥ 5% All Grades) in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=403</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>37</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>1.6</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>63</td>
<td>1.1</td>
</tr>
</tbody>
</table>

\[ \text{\textsuperscript{2}} \text{ Does not reflect fasting values} \]

Cerebrovascular and Ischemic Cardiovascular Events

ERLEADA and 1% of patients treated with placebo. It is unknown whether anti-epileptic medications will be effective if a patient develops a seizure during treatment. It is recommended that patients be evaluated for fall risk.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and 7% of patients treated with placebo. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

The safety and efficacy of ERLEADA have not been established in females. There are no data on the clearance or use of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day; decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (ossification delays, supernumerary short thoracolumbar ribs), and small, incomplete ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 8 times, respectively, the AUC in patients.

Risk Summary

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. [See Use in Specific Populations].

Preclinical Use

Safety and effectiveness of ERLEADA in pediatric patients has not been established.

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 to 74 years, and 40% were 75 years and older.

In patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

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

Cerebrovascular and Ischemic Cardiovascular Events

- Inform patients that ERLEADA has been associated with cerebrovascular and ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular or cerebrovascular event occur [see Warnings and Precautions].

- Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions].

- Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions].

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.

- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.

- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

- Instruct patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets [see Dosage and Administration (2.1) in Full Prescribing Information].

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions].

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations].

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cp-50101v7
NUMEROUS THERAPEUTIC OPTIONS are available for the treatment of follicular lymphoma (FL) but identifying the ideal sequence of therapies, especially when considering later lines of treatment such as chimeric antigen receptor (CAR) T-cell therapy, make it difficult for CAR T-cell therapy to find its optimal place in the armamentarium.

"Follicular lymphoma is different from diffuse large B-cell lymphoma [DLBCL]...in that most of these patients have an indolent disease, and a relapse in follicular lymphoma does not mean you have to treat the patient right away," Jose Sandoval-Sus, MD, assistant member of the Moffitt Malignant Hematology and Cellular Therapy at Memorial Healthcare System at Moffitt Cancer Center in Pembroke Pines, Florida, said in an interview with Targeted Therapies in Oncology™.

"The patient can relapse and be without a second line of therapy for months or even years." As such, the timing and order of treatments for FL may vary from that of other lymphomas.

Current Therapies

Although the combination of rituximab (Rituxan) and chemotherapy have improved survival outlook for patients with FL, the need to identify effective later lines of therapy and unique combinations remains. For example, the combination of bendamustine HCl (Bendeka) with rituximab has resulted in improved median progression-free survival (PFS) and associated toxicities compared with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and rituximab, cyclophosphamide, vincristine, and prednisone (R-CHP), leading to a preference for the doublet as first-line therapy. Another available anti-CD20 monoclonal antibody is obinutuzumab (Gazyva), which has a similar response rate and overall safety profile to rituximab, but its higher toxicity profile is a concern when used with CHOP or bendamustine, so it is recommended in the second-line setting at this time.

Other combinations including immunomodulators such as lenalidomide (Revlimid) and PI3K inhibitors such as idelalisib (Zydelig), duvelisib (Copiktra), copanlisib (Aliqopa), and umbralisib (Ukonig) are available for patients with relapsed or refractory (R/R) FL. Currently, the only CAR T-cell therapy with FDA approval in R/R FL as a whole is axicabtagene ciloleucel (axi-cel; Yescarta). Lisocabtagene maraleucel (liso-cel; Breyanzi) is approved for grade 3b R/R FL specifically. Tisagenlecleucel (tisa-cel; Kymriah) is another prominent CAR T-cell therapy that has been granted priority review in R/R FL and is approved for use in R/R B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

Drug Interactions

Bendamustine

There is concern that the early use of bendamustine may present obstacles to the later use of CAR T. In particular, bendamustine’s lymphodepleting properties could affect the timing required to manufacture CAR T cells. Marked reductions in CD3+ and CD3+CD4+ T cells were observed during induction with bendamustine in combination with obinutuzumab and rituximab in the GALLIUM study (NCT01332968). Two other studies evaluating bendamustine-rituximab found a greater sustained and pronounced depletion in CD4+ and CD8+ T cells compared with R-CHOP.

"The concern is that using bendamustine-based regimens could limit the quality and quantity of CAR T cells when manufacturing the therapy," Sandoval-Sus said.

The choice of lymphodepleting agent was explored in the phase 2 JULIET trial (NCT02443248). In the trial, investigators chose cyclophosphamide/ fludarabine or bendamustine as lymphodepleting agents prior to tisa-cel administration. A total of 103 patients (93%) received the lymphodepleting...
Chimeric antigen receptor (CAR) T-cell therapy is an attractive new therapeutic approach for many cancer types, especially hematologic malignancies such as follicular lymphoma. However, with so many treatment options and a lack of data on sequencing, it could be difficult for CAR T-cell therapy to find its optimal place.

chemotherapy, with 73% receiving the combination of cyclophosphamide/fludarabine. A total of 24 patients (20%) received bendamustine, and the 3-month PFS estimate was 52% (95% CI, 30%-70%), with a suggested improvement seen in the rate of cytopenias.

Studies in R/R Hodgkin lymphoma suggest that bendamustine with fludarabine is a preferred lymphodepletion modality prior to initiation of CAR T-cell treatment. More data are needed to determine the exact impact bendamustine has on CAR T cells.

**PI3K Inhibitors**

The relationship between PI3K inhibitors and CAR T cells appears positive. Recent data suggest the expansion of T cells is significantly increased when PI3K inhibitors are added to CAR T-cell therapy.

For example, in a phase 1 escalation and expansion trial (NCT03274219) presented during the 2020 American Society of Hematology (ASH) Annual Meeting, investigators enriched the CAR product bb21217 with the addition of the PI3K inhibitor bb007. Investigators observed an improved response and extended duration of response (DOR) compared with non-enriched CAR T cells in patients.

In a preclinical study, T cells were successfully expanded from patients with heavily pretreated lymphoma, resulting in increased frequencies of CD8 cells and costimulatory molecule-expressing cells. This ultimately led to

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When considering the sequence of therapy for optimal outcomes in FL, the benefits and risks of each approach and goals for therapy should be explored with patients.
Follicular Lymphoma

greater in vivo expansion and antitumor activity.14 Another in vivo study determined that PI3K inhibition ultimately enhanced the durability of CAR T cells, improving in vivo persistence and reducing tumor burden.15 Approval for PI3K inhibitors in FL is currently based on phase 2 trial data, making selection difficult.

“Umbralisib is perhaps my treatment of choice right now,” Sandoval-Sus said. “Although we should never compare between trials, the [adverse] effects appear a little more generous. The overall response, complete response, and PFS rates are all similar.”

CAR T-Cell Toxicities

There is certainly an understandable concern for toxicities given that the boxed warning on all approved CAR T-cell therapies includes risks for cytokine release syndrome (CRS) and neurologic toxicity. Initially, the grading of CRS and toxicity management was not standardized, making it difficult to compare safety profiles of different CAR T-cell therapies.16 The American Society for Transplantation and Cellular Therapy released consensus guidelines in 2019 to further simplify CRS grading.17,18 Neurotoxicity can occur with CRS or independent of CRS. Neurotoxicity resulting in fatal cerebral edema has been reported, and all were associated with concomitant CRS.16 Several cancer organizations have since released consensus guidelines on the management of toxicities related to CAR T-cell therapy use, including the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer.19,20

Preemptive use of anti-IL-6 agents such as tocilizumab (Actemra) and corticosteroids are an often-used approach.16 Additionally, the safety profile of later-generation CAR T-cell therapies have improved, with lower rates of grade 3 or higher CRS and neurotoxicity reported in the ELARA (NCT03568461) and ZUMA-5 (NCT03105336) trials.21,22

**Axi-cel**

Axi-cel was granted accelerated approval by the FDA for treatment of adult patients with R/R FL after 2 or more prior lines of systemic therapy based on results from the phase 2 ZUMA-5 trial.4 Specifically in patients with FL, the trial showed an overall response rate of 94% (95% CI, 87%-98%) by independent central review with axi-cel. Seventy-six percent of patients had a complete response.22 Neither the median progression-free survival, overall survival, nor the median DOR were reached at the time of data cutoff in the cohort.22 Grade 3 or higher CRS was reported in 6% of patients with FL and grade 3 or higher neurologic toxicity in 15%.22,23

**Tisa-cel**

Primary analysis from the phase 2 ELARA trial indicates tisa-cel resulted in an overall response rate of 86% (95% CI, 78%-92%) and a complete response rate of 66% (95% CI, 56%-75%) with 1-time infusion in patients with R/R FL. Most patients were heavily pretreated, and no patients in the trial experienced a grade 3 or higher CRS (FIGURE).21 This trial included patients who had R/R FL after receiving 2 or more lines of therapy or after failing autologous stem cell transplantation.

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**FIGURE. STUDY DESIGN FOR ELARA (NCT03568461)**

- **Key eligibility criteria**
  - ≥18 years of age
  - FL grade 1, 2, or 3A
  - Relapsed/refractory disease
  - No evidence of histological transformation/FL3B
  - No prior anti-CD19 therapy or allogeneic HSCT

- **Study treatment**
  - Lymphodepleting chemotherapy options were:
    - Fludarabine + cyclophosphamide
    - Bendamustine
    - Tisagenlecleucel dose range (single IV infusion) was: 0.6-6 × 10⁸ CAR-positive viable T cells

- **End points**
  - Primary: CRR by IRC (Lugano classification 2014)
  - Secondary: ORR, DOR, PFS, OS, safety, cellular kinetics

CAR, chimeric antigen receptor; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; IRC, independent review committee; OS, overall survival; PFS, progression-free survival
cell transplantation with a median of 4 prior lines of therapy (range, 2-13). Neutropenia (28%) and anemia (13%) were the most common grade 3 or higher adverse events among the 97 patients evaluable for safety. CRS of any grade was observed in 49% of patients (grade 2, 12%; grade 3, 3%; grade 4, 1 patient who recovered). These data show the promise of tisa-cel in patients with R/R FL, but further meta-analysis and trials are needed to determine proper patient selection.

Sandoval-Sus noted that “the ELARA study was fairly similar to the ZUMA-5 study, which led to axi-cel’s approval. Though there were some differences in the study populations, there were similar numbers of patients with progression of disease within 24 months (POD24), which is a very established high-risk follicular lymphoma population.”

**Liso-cel**

The FDA approved liso-cel for treatment of adult patients with R/R large B-cell lymphoma (LBCL) after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3b. Approval was based on the ongoing TRANSCEND-NHL-001 trial (NCT02631044). A total of 344 adult patients with R/R LBCL of various histological subgroups, including FL, were included, and 269 of them received at least 1 dose of liso-cel; 256 patients were evaluable for efficacy. Patients had a median of 3 prior lines of therapy (range, 1-8), with 97% having had at least 2 previous lines of therapy. The objective response rate was 73% (95% CI, 66.8%-78.0%), and the complete response rate was 53% (95% CI, 46.8%-59.4%). The most common grade 3 or higher adverse events included neutropenia (60%), anemia (37%), and thrombocytopenia (27%). CRS was observed in 42% of patients (grade 3, 2%), with neurological events observed in 30% (grade 3, 10%).

Another ongoing phase 2 trial, TRANSCENDWORLD (NCT03484702) is evaluating the efficacy and safety of liso-cel in adults with aggressive B-cell non-Hodgkin lymphoma (NHL), including grade 3b FL. More data are needed to determine the true impact on FL as a whole.

**Other Emerging Therapeutic Options**

**Bispecific Antibodies**

The development and promising rates of durable remission associated with CAR T cells, along with the potential for bispecific antibody use in CAR T-cell failure, has turned the spotlight back toward this technology as a possible therapy.

**Glofitamab**

Glofitamab is a novel, T-cell- engaging bispecific antibody that has a longer half-life compared with non-Fc-bearing bispecific T-cell engagers and targets CD20. The configuration enables bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells. Updated analysis from a phase 1/2 study evaluating patients with multiple R/R FL treated with glofitamab as monotherapy or in combination with obinutuzumab was presented by Franck Morschhauser, MD, PhD, professor of hematology and head of the Lymphoma Unit, Centre Hospitalier Universitaire de Lille, in France, during ASH 2021. The complete metabolic response (CMR) rate ranged from 7% to 33% for the 3 monotherapy cohorts and was 74% for the combination cohort. Median follow-up of CMR ranged from 0-14 months (monotherapy) and 0–5 months (combination). An 81% overall response rate was observed in the 53 patients receiving monotherapy, and a 100% overall response rate was observed in the combination arm. At a median follow-up of 4.4 months (95% CI, 3.5–8.6), the CMR rate was 70% in the monotherapy arm, and it was 74% at a median follow-up of 5.5 months (95% CI, 5.4–6.3) in the combination arm.

**Mosunetuzumab**

Mosunetuzumab is another bispecific antibody of interest in the treatment of R/R FL. The agent targets CD20 (B cells) and CD3 (T cells), redirecting T cells to engage and eliminate malignant B cells. It is currently being evaluated in a phase 1/2 study (NCT02500407). Results from the phase 1 dose-escalation portion revealed high activity and a favorable safety profile for mosunetuzumab in patients with R/R FL who had received 2 or more previous lines of therapy.

Updated results from the phase 2 expansion cohort were presented at ASH 2021 by Elizabeth Budde, MD, PhD, City of Hope Comprehensive Cancer Center in Duarte, California. A total of 90 patients with R/R FL who had received 2 or more prior lines of therapy were included. Results included a complete response (CR) rate of 60% (95% CI, 49%-70%) and an objective response rate of 80% (95% CI, 70%-88%) per independent review facility. Median duration of response was 22.8 months (95% CI, 9.7–not evaluable), and median PFS was 17.9 months (10.1–not evaluable). The CR rate for patients with POD24 disease was 57% (95% CI, 42%-72%) versus 63% (95% CI, 47%-77%) for those without. CRS was observed in 44.4% of patients but was mostly grade 1 (25.6%) or grade 2 (16.7%), with 1 patient each experiencing grade 3 and grade 4 CRS. All CRS events resolved.

Sandoval-Sus sees great potential with bispecific antibodies in FL. “In my opinion, bispecific antibodies will be one of the major competitors of CAR T cells, specifically in follicular lymphoma, but we certainly need more information and need to learn how to properly use them.”

**Looking Forward**

Although FL remains a disease that is rarely curable, Sandoval-Sus is encouraged about future potential treatments for patients with FL.

“I am looking forward to the outcome of tisa-cel and the likely FDA approval. I am also very eager to see the follow-up results of the bispecific antibodies. If we have medications [that] can be given safely and with excellent responses, it will be interesting to see what happens in the future with both therapies,” he said.

He added that he is also interested in future trials involving CAR T-cell therapy in combination with PI3K and EZH2 inhibitors in the hope that combinations may provide improved quality of response and decreased toxicities.

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References are available on TargetedOnc.com.
ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status.¹⁻⁴

**Indication**

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

**Important Safety Information**

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

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

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

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

**HRd POPULATION**
(n=373)

**Reduction in the risk of progression or death**

<table>
<thead>
<tr>
<th><strong>OVERALL POPULATION</strong></th>
<th><strong>HRd POPULATION</strong></th>
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<tbody>
<tr>
<td>MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR, 0.62; 95% CI, 0.50-0.76) P&lt;0.0001</td>
<td>MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO (HR, 0.43; 95% CI, 0.31-0.59) P&lt;0.0001</td>
</tr>
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**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 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.

**Important Safety Information (continued)**

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

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

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

Visit ZEJULAHCP.COM to explore the PRIMA data

Trademarks are property of their respective owners.
1.3 Treatment of Advanced Ovarian Cancer after 3 or More Lines of Platinum-Based Chemotherapy.

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

1.4 Treatment of Recurrent Ovarian Cancer

ZEJULA is indicated for the treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) status defined by either:

- a deleterious or suspected deleterious BRCA mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

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

1. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) including cases with fatal outcome, have been reported in patients who received monotherapy with ZEJULA in clinical trials. In 1,785 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 0.5% (8/1,785). The duration of therapy with ZEJULA in patients who developed secondary MDS/AML therapy-related AML varied from 0.4 months to 4.9 years. All of these patients had received previous chemotherapy with platinum agent and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

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

In PRIMA, the overall incidences of Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count: Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 23%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 5%, 3%, and 3%, respectively, of patients.

In NOVA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients. In QUADRA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 26%, 27%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients.

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

5.3 Hypertension and Cardiovascular Effects

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

In PRIMA, Grade 4 to 6 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 551 days) and with a median duration of 12 days (range: 1 to 61 days). There were no DLTs due to hypertension.

In NOVA, Grade 3 to 6 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 <3% of patients.

In QUADRA, Grade 4 to 6 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% to 0.3%.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and then periodically thereafter during treatment with ZEJULA. Close 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 Nonclincial Toxicology (13.2) of full prescribing information).

Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Aprosire pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception (see Use in Reproductive Capabilities (8.9, 8.31)).

5.6 Allergic Reactions to F(ab)2 Yellow No. 5 (Traztazine)

ZEJULA capsules contain F(ab)2 Yellow No. 5 (traztazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of F(ab)2 Yellow No. 5 (traztazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS

The following ADVERSE REACTIONS are described elsewhere in the labeling:

- Myelosuppression (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 QUADRA trials were nausea (63%), vomiting (59%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypoglycemia (11%).

andard Phase III randomized, controlled clinical trials of platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA the median duration of treatment was 11.1 months (range: 0.3 to 59 months).

All Patients Receiving ZEJULA in PRIMA—Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in patients treated with ZEJULA included thrombocytopenia (16%), anemia (13%), and nausea and neutropenia (12%).

Serious adverse reactions in patients treated with ZEJULA included thrombocytopenia (16%), anemia (13%), and nausea and neutropenia (12%).

All adverse reactions reported in ≥1% of any treatment group in PRIMA and NOVA are listed below. The occurrence of adverse reactions is summarized by type of reaction and by decreasing order of frequency.

Blood and lymphatic system disorders

- Thrombocytopenia
- Anemia
- Neutropenia
- Leukopenia

Gastrointestinal disorders

- Nausea
- Constipation
- Vomiting

Cardiovascular disorders

- Hypertension

Metabolism and nutrition disorders

- Decreased appetite

Musculoskeletal and connective tissue disorders

- Musculoskeletal pain

Nervous system disorders

- Headache
- Dizziness

Psychiatric disorders

- Insomnia

Renal and urinary disorders

- Acute kidney injury
- Respiratory, thoracic and mediastinal disorders
- Cough

Vascular disorders

- Hypertension

(continued on next page)
Patients receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA Among patients who received ZEJULA with the dose based on weight or platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (17%). Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZEJULA.

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>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEJULA (%)</td>
<td>Placebo (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
<td>21</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 4: Adverse Reactions Reported in ≥25% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEJULA (%)</td>
<td>Placebo (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>74</td>
<td>35</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>57</td>
<td>41</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

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

Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 290 days.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEJULA (%)</td>
<td>Placebo (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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</tr>
<tr>
<td>Decreased appetite</td>
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<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
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<tr>
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<td>13</td>
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<tr>
<td>Psychiatric disorders</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

Common Terminology Criteria for Adverse Events version 4.02. Includes neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 290 days.

Table 6: Adverse Reactions Reported in ≥25% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
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</tr>
<tr>
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<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
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<td></td>
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<td>14</td>
</tr>
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<td>Renal and urinary disorders</td>
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<tr>
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Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies

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

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

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Fatal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZEJULA. Serious adverse reactions in >3% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1 to 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (>5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

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

(continued on next page)
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: Pancreatitis.

Immune System Disorders: Hypersensitivity (including anaphylaxis).

Psychiatric Disorders: Confusional state/disorientation, hallucination, cognitive impairment (e.g., memory impairment, concentration impairment).

Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

Skin and Subcutaneous Tissue Disorders: Photosensitivity.

Vascular Disorders: Hypertensive crisis.

8.5 Renal and Cardiovascular Effects

Prevalent and post-marketing 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.

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Respiratory, Thoracic, and Mediastinal Disorders: Non-infectious pneumonitis.

Skin and Subcutaneous Tissue Disorders: Photosensitivity.

Vascular Disorders: Hypertensive crisis.
cytotoxicity further enhanced by cetuximab. The single-arm, multicenter, multicohort IPH2201-203 trial was the first study to explore the triplet combination. The trial consisted of a dose escalation portion, followed by 3 expansion cohorts for patients with SCCHN. Cohort 3 added monalizumab.

In this cohort, patients with recurrent/metastatic SCCHN were enrolled who had no prior systemic therapy in this setting. Participants were enrolled regardless of their PD-L1 or human papillomavirus (HPV) status.

The primary end point of the cohort was ORR by RECIST criteria, and the key secondary end points included safety, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

The confirmed ORR was 32.5% (95% CI, 20%-48%). When including unconfirmed responses, the rate went up to 50% (95% CI, 35%-65%). Complete responses were reported in 3 patients, partial responses in 10, and stable disease in 22. Four patients experienced progressive disease and 1 had an early death and was not evaluable. “There were quite a few responders who had very deep response, even some with complete response,” Colevas said. “These responses were not short-lived.”

At a median follow-up of 16.3 months (range, 4.4-25.7), the median PFS was 6.9 months (95% CI, 4.4-9.3) and the median OS was 15 months (95% CI, 11.4-not available [NA]). At 12 months, the OS rate was 58.6% (95% CI, 45%-77%) and 7 of 13 patients had ongoing response, with the longest lasting 19.5 months. The median DOR was NA (95% CI, 7.1-NA).

In previous results from another cohort of the study, treatment with the doublet of monalizumab and cetuximab demonstrated promising activity in patients with recurrent or metastatic SCCHN. In 40 treated patients with prior immunotherapy treatment, the objective response rate (ORR) was 20% (95% CI, 10.5%-34.8%).2

An exploratory analysis was performed through response by PD-L1 CPS levels, and responses were seen in patients with both positive and negative PD-L1 status. However, Colevas cautioned that as there were small subsets of patients, especially those with CPS less than 1, the results should be interpreted with caution and are not actionable for selecting patients who would benefit from this regimen.

Treatment-emergent AEs were reported in all patients, with the most common, of any grade, being dermatitis acneiform, paronychia, fatigue, pruritus, and hypomagnesemia. Grade 3 or higher events were observed in 72% of patients, with 48% being drug related. AEs led to discontinuation of a drug in 12% of patients and discontinuation of all 3 drugs in 5%. AEs led to death in 8%, but none of these events were considered related to treatment.

Colevas said there were no new safety signals identified in the preliminary results of the cohort. He concluded that these data support further evaluation of the triplet regimen of monalizumab, cetuximab, and durvalumab in the SCCHN population.

**REFERENCES**


THE NOVEL ANTI-PD-L1 antibody TQ-B2450 in combination with anlotinib, a multitargeting tyrosine kinase inhibitor, led to an improvement in efficacy over immunotherapy alone in previously treated patients with advanced non-small cell lung cancer (NSCLC), according to results from a double-blind, randomized phase 1 trial (NCT03910127) presented during the European Society for Medical Oncology Immuno-Oncology Congress 2021. “PFS [progression-free survival] and ORR [objective response rate] with TQ-B2450 combined with anlotinib were significantly improved compared with the control group [in patients with advanced NSCLC],” said Baohui Han, MD, PhD, professor of respiratory medicine at Shanghai Chest Hospital of Shanghai Jiao Tong University in China. “TQ-B2450 combined with anlotinib may be a promising treatment for advanced NSCLC.”

Enrolled patients had stage IIIB-IV NSCLC, an ECOG performance status of 0 or 1, and received at least 1 line of chemotherapy but had failed or were intolerant to treatment. Additionally, patients were EGR and ALK wild type and were not restricted by PD-L1 tumor proportion score (TPS) levels.

A total of 101 patients were randomized equally between 3 treatment arms: TQ-B2450 at 1200 mg intravenously (IV) on day 1 of each 21-day cycle plus anlotinib at 12 mg daily on days 1 to 14 of the cycle, TQ-B2450 at 1200 mg IV and anlotinib at 10 mg daily, or TQ-B2450 at 1200 mg IV plus placebo. Treatment continued until progressive disease or intolerance to treatment. However, the 2 doublet arms were later combined (n = 68) and compared with the monotherapy arm (n = 33), as the average daily exposed dose of anlotinib was 10.2 mg.

The primary end point was PFS, and secondary end points included safety, ORR, disease control rate (DCR), duration of response (DOR), and overall survival.

In the merged combination arm, the median age was 61.5 years (range, 30-73), 69.12% were men, 93.59% had an ECOG performance status of 1, and 60.29% were former smokers. The most common pathology was adenocarcinoma in 63.24% of patients followed by squamous cell carcinoma in 20.59%, but was unknown in 16.18%. Most patients had stage IV disease (80.88%), no brain metastases (86.67%), and positive PD-L1 expression (88.37%).

In the monotherapy arm, the median age was 60 years (range, 47-77), 81.82% were men, 93.94% had an ECOG performance status of 1, and 66.67% were former smokers. A total of 63.64% of patients had adenocarcinoma vs squamous cell carcinoma pathology in 27.27%, and 82.76% had stage IV disease. Brain metastases were reported in 27.27%, and 79.27% had positive PD-L1 TPS of 1% or higher.

Across prespecified subgroups, PFS favored the doublet included hypertension (18.18%). Only 1 grade 3/4 was reported in treatment-related events of any grade in the combination arm and in all but 2 in the monotherapy arm. In the doublet arm, 92.65% of events were considered TQ-B2450 related and 94.12% were considered related to anlotinib. Grade 3 or higher treatment-emergent AEs were reported in 67.65% and serious AEs in 41.18%. Anlotinib dosing was disrupted in 33.82% of patients, adjusted in 22.06%, and discontinued in 20.59%. In the monotherapy arm, 84.85% of patients had treatment-related AEs, grade 3 or higher events were reported in 21.21%, and serious AEs in 15.15%.

The most common treatment-related AEs of any grade in the combination arm were hypertension (48.53%), hypertriglyceridemia (42.65%), increased aspartate aminotransferase levels (35.29%), increased thyroid-stimulating hormone levels (35.29%), and increased alanine aminotransferase (ALT) levels (32.35%). Common grade 3/4 AEs with the doublet included hypertension (19.12%) and hypertriglyceridemia (8.82%).

With single-agent TQ-B2450, the most common treatment-related events of any grade were anemia (24.24%), hyperglycemia (24.24%), increased ALT levels (21.21%), and loss of appetite (18.18%). Only 1 grade 3/4 was reported in the monotherapy arm of hypertension.

Han noted that a randomized, controlled phase 3 trial (NCT04964479) is ongoing, exploring the combination of TQ-B2450 and anlotinib vs pembrolizumab (Keytruda) in the treatment of patients with advanced NSCLC and positive PD-L1 expression. TT
Pembrolizumab/Chemotherapy Combo Shows Positive Responses in Neoadjuvant Setting of ESCC

By Tony Berberabe, MPH

In the neoadjuvant setting, the combination of pembrolizumab (Keytruda), paclitaxel, and cisplatin demonstrated responses and safety in an interim analysis of the phase 2 KEYSTONE-001 trial (NCT04389177), which evaluated patients with locally advanced resectable esophageal squamous cell carcinoma (ESCC).1 Findings were presented during a virtual presentation at the European Society of Medical Oncology Immuno-Oncology Congress 2021 by lead author Xiaobin Shang, MD, an attending surgeon in the Department of Minimally Invasive Esophageal Surgery at Tianjin Medical University Cancer Institute & Hospital in China.1

Tumor responses were encouraging, with the pathologic complete response (pCR) reported as 41.4% in 12/29 patients with stage TON0 disease and 58.6% (17/29) in patients with ypT0 (absence of invasive cancer in breast and axillary nodes). The PR for neoadjuvant measures was 72.4% of patients (21/29).2 Regarding T stage, 58.6% of patients were ypT0, 17.2% were ypT1, 13.8% were ypT2, and 10.4% were ypT3. Similarly, for N stage, 62.1% of patients were ypN0, 20.7% were ypN1, 13.8% were ypN2, and 3.4% were ypN3.

The standard of care consists of neoadjuvant chemoradiotherapy with surgery for locally advanced disease. However, patients often refuse or abandon radiotherapy because of adverse events (AEs).2 The investigators sought to determine the efficacy of pembrolizumab administered in the neoadjuvant setting prior to surgery.

Patients were eligible to enroll if they had stage III disease, no previous history of treatments, and had an ECOG performance status of 0 to 1. Fifty patients were randomized to receive intravenous pembrolizumab (500 mg on day 1), paclitaxel (135 mg/m² on day 2), and cisplatin (20 mg/m² on days 2 to 4). Treatment was delivered every 3 weeks over the course of 3 cycles. After 4 to 6 weeks, patients underwent robotic-assisted McKeown surgery. The investigators said patients with pCR were observed and received follow-up, whereas patients with non-pCR received pembrolizumab as single-agent maintenance for at least 6 cycles. The primary end points were major pathologic response rate and safety, and secondary end points were pCR, objective response rate, and quality-of-life assessment.

At this interim analysis, 42 patients were enrolled, of which 29 completed surgery and were evaluated. At baseline, patients were a median age of 61 years (range, 46-70), the majority (93.1%) were men, and 93.1% had an ECOG performance status of 1. Investigators said all patients completed the prescribed 3 cycles of pembrolizumab and chemotherapy without treatment interruption or disruption. The median time from the first dose of pembrolizumab to surgery was 79 days (interquartile range, 75-83).

Regarding safety, no AEs of grade 3 or higher that were related to neoadjuvant treatment occurred. The most common AEs related to neoadjuvant treatment were rash or pruritus (62.1%), leukopenia (51.7%), dry skin (44.8%), and xerostomia (34.5%). The total incidence of surgery-related AEs was 17.2% and included infectious pneumonia (6.9%) and anastomotic leakage (10.4%).

To determine health-related quality of life, patients completed 2 questionnaires: the European Organization for Research and Treatment Quality of Life Questionnaires-Core30 (QLQ-Q30) and the QLG-Oesophagus 18 (QLQ-OES18). Findings from the QLG-C30 questionnaire suggested that patients who underwent neoadjuvant therapy had a lower risk of deterioration in both function and symptoms. The QLG-OES18 questionnaire suggested that neoadjuvant therapy was associated with a lower risk of worsening of 10 symptoms, including choking, coughing, dry mouth, trouble swallowing, and eating.

These findings are encouraging, and the investigators reported that KEYSTONE-002 (NCT04807673), evaluating pembrolizumab combined with chemoradiotherapy vs concurrent chemoradiotherapy in the neoadjuvant setting in locally advanced ESCC, is ongoing.

REFERENCES


Sunitinib is an FDA-approved, second-line treatment for patients with imatinib mesylate (Gleevec)-refractory or -intolerant GIST. However, research evaluating sunitinib has demonstrated a median PFS of only 5.6 months.²

“Ripretinib is indicated for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more tyrosine kinase inhibitors, including imatinib. In a phase 1 study, the median PFS for ripretinib as the second-line therapy was 10.7 months,” Michael H. Heinrich, MD, said during the ASCO plenary. Heinrich is a professor of medicine at the Oregon Health & Science University School of Medicine in Portland.

Therefore, in the interventional, randomized, multicenter, open-label phase 3 INTRIGUE trial, Heinrich and colleagues aimed to determine if ripretinib would be superior to sunitinib for the treatment of patients with advanced GIST who were previously treated with imatinib.

Patients with confirmed advanced GIST who were at least aged 18 years and progressed on or were intolerant to imatinib were enrolled. A total of 453 patients were randomized 1:1 to receive either ripretinib 150 mg once daily (n = 226) or sunitinib 50 mg once daily (n = 227). Patients were stratified by mutational status (KIT exon 11, KIT/PDGFRA wild type, or other PDGFRA mutations) and intolerance to imatinib.

The investigators primarily assessed for PFS by independent radiographic review in the overall KIT exon 11 intention-to-treat (ITT) population vs the all-patients (AP) ITT population.

The secondary end points evaluated in the study were ORR by independent review and overall survival in the KIT exon 11 ITT population vs the AP ITT population.

Of the 453 patients randomized, 223 from the ripretinib arm and 221 from the sunitinib arm received at least 1 dose of treatment (TABLE1). At the time of data cutoff, treatment was ongoing for 65 patients in the ripretinib arm and 52 in the sunitinib arm.

The population had a median age of 60 years (range, 18-88), 62% of patients were male, and 66.2% were White. The majority of patients were from Europe (46.8%), followed by North America (36.0%), Asia-Pacific (13.2%), and South America (4.0%).

Disease characteristics screened at baseline showed that 57.2% of patients had an ECOG performance score of 0 and 41.9% had a score of 1; the remaining patients had a score of 2. KIT exon 11 mutations were most common among patients (72.2%), followed by KIT exon 9 (13.2%). More than 9% of patients in the study had intolerance to imatinib.

The sum of the longest diameters of target lesions among the patients was 90.5 mm (range, 11-456). According to the Kaplan-Meier estimate for survival, in the KIT exon 11 ITT group, the median PFS was 8.3 months (95% CI, 6.8-13.3) with ripretinib compared with 7.0 months (95% CI, 5.6-10.9) with sunitinib (HR, 0.88; 95% CI, 0.66-1.16; P = .36).

In the AP ITT population, the median PFS with ripretinib was 8.0 months (95% CI, 6.5-10.8) versus 8.3 months (95% CI, 6.3-11.0) with sunitinib (HR, 1.05; 95% CI, 0.82-1.33; nominal P = .72).

*For the overall population, the hazard ratio was 1.05. The confidence intervals for all of the stratification subgroups showed no clear difference.
between the treatment arms, [except for] patients with KIT exon 9-mutant GIST, in which sunitinib treatment appeared to provide a PFS benefit compared with repetitive treatment,” Heinrich explained.

The ORR shown with ripretinib in the KIT exon 11 population was 23.9% (95% CI, 16.5%-27.6%) versus 17.6% (95% CI, 12.9%-23.2%) with sunitinib. Again, responses to ripretinib were largely partial, with 1 complete response (CR); there were 3 CRs in the sunitinib group. The overall difference in ORR was 4.2% (95% CI, −3.2 to 11.5; P = .27).

Any-grade treatment-emergent adverse events (TEAEs) were observed in 99.1% of patients in the ripretinib arm compared with 99.1% in the sunitinib arm. Grade 3 and 4 TEAEs were seen in 41.3% of the ripretinib arm versus 65.6% of the sunitinib arm, and serious TEAEs occurred in 7.0% versus 9.9%, respectively. More dose reductions, dose interruptions, treatment discontinuations, and TEAEs leading to death occurred in the sunitinib arm than the ripretinib arm.

In the ripretinib arm, the most common any-grade TEAEs in the sunitinib arm were palmar-plantar erythrodysesthesia (51.1%), diarrhea (48.0%), hypertension (47.1%), fatigue (41.2%), and stomatitis (36.2%).

“Ripretinib is still a very good drug, with excellent tolerability and reasonably good activity against advanced GIST, regardless of KIT mutational status.”

—GEORGE D. DEMETRI, MD

Any-grade treatment-emergent adverse events (TEAEs) were observed in 99.1% of patients in the ripretinib arm compared with 99.1% in the sunitinib arm. Grade 3 and 4 TEAEs were seen in 41.3% of the ripretinib arm versus 65.6% of the sunitinib arm, and serious TEAEs occurred in 7.0% versus 9.9%, respectively. More dose reductions, dose interruptions, treatment discontinuations, and TEAEs leading to death occurred in the sunitinib arm than the ripretinib arm.

In the ripretinib arm, the most common any-grade TEAEs were alopecia (64.1%), fatigue (37.7%), myalgia (36.3%), and constipation (35.0%). The most common

any-grade TEAEs in the sunitinib arm were palmar-plantar erythrodysesthesia (51.1%), diarrhea (48.0%), hypertension (47.1%), fatigue (41.2%), and stomatitis (36.2%).

Treatment tolerability in the INTRIGUE trial was based on patient-reported measures. “Fewer patients receiving ripretinib experienced a moderate to an extremely large impact on their lives due to skin toxicity across the treatment cycles compared with sunitinib,” Heinrich stated.

Heinrich noted that despite missing its primary end point, the research shows that the ORR benefit and tolerability of ripretinib make it a solid candidate for the treatment of advanced GIST in patients who failed or who developed intolerance to imatinib.

During a postpresentation discussion about the INTRIGUE data, Demetri stated. “Ripretinib is still a very good drug with very good activity against advanced GIST, but with some annoying, yet manageable toxicities.”

REFERENCES

FIGURE. PATIENT DISPOSITION FOR THE INTRIGUE TRIAL (NCT03673501)\(^1\)

[Diagram showing patient disposition for the INTRIGUE trial]
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.
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 1.4%. 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. If 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.

Adverse effects are usually mild to moderate in severity and generally manageable with appropriate adjustment of treatment. However, serious adverse reactions may occur during treatment with BLENREP. Therefore, it is important to be aware of the potential adverse reactions associated with BLENREP.

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 70 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 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 × ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
Changes in visual acuity may be associated with difficulty for driving and reading.

Monitoring and Patient Instruction

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

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (6.2)].

1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication is approved under accelerated approval based on response rate [see Clinical Studies (14) of full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

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

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infectious 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% 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% in 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 83 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%. Of the patients with decreased visual acuity of worse than 20/40, 38% 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 Thromboctopenia

Thromboctopenia 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 thromboctopenic event was 26.5 days. Thromboctopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 or 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 Embryofetal 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, MMAF) and it targets actively dividing cells.

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

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

Serious adverse reactions in >3% of patients included pneumonia (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>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Keratopathy*</td>
<td>71 44</td>
</tr>
<tr>
<td>Decreased visual acuity*</td>
<td>53 28</td>
</tr>
<tr>
<td>Blurred vision†</td>
<td>22 4</td>
</tr>
<tr>
<td>Dry eyes†</td>
<td>14 1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22 3</td>
</tr>
<tr>
<td>Fatigue†</td>
<td>20 2</td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions†</td>
<td>21 3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 2</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12 0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection†</td>
<td>11 0</td>
</tr>
</tbody>
</table>

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.
† Visual acuity changes were determined upon eye examination.
‡ Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
§ Dry eyes included dry eye, ocular discomfort, and eye pruritus.
∥ Fatigue included fatigue and asthenia.
¶ Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.
‖ Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

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

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62 21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49 22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32 18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28 9</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57 2</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43 4</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38 3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28 5</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26 1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>23 5</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22 1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21 2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20 2</td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 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 genotoxix 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.

(continued on next page)
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 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)].
Digital Monitoring With PROs Improves Patient QOL

By Sara Karlovitch

Patient-reported outcomes (PROs) that are monitored digitally may help to improve symptom control, physical function, and health-related quality of life (QOL), according to a presentation given during the American Society of Clinical Oncology Plenary Series: November 2021 Session.

According to presenter Ethan Basch, MD, MSc, there are many barriers and challenges to the usual approach to symptom monitoring in the community setting. On the clinical side, there is limited time during an office visit to discuss symptoms and symptom management. During that session, there are often competing priorities. On the patient side, there is often a reluctance to contact their care providers until symptoms grow worse or they have problems connecting with the center. Research has shown that clinicians miss up to 50% of symptoms, potentially leading to consequences downstream, including hospitalization, treatment holds, and preventable suffering.

“Those communication hurdles inhibit the ability of clinicians to detect and react early to symptoms before they worsen. An alternative approach is to use digital symptom monitoring with patient-reported outcomes,” said Basch, the Richard M. Goldberg Distinguished Professor in Medical Oncology; professor of public health; health policy, and management at the Gillings School of Global Public Health; and director of Cancer Outcomes Research Program; and chief of oncology at the University of North Carolina at Chapel Hill.

An alternative to traditional practices is digital symptom monitoring using electronic PROs. With this method, an electronic reminder is sent to patients, who then report symptoms. This results in either an email alert or a report for providers.

A prior single-center study, STAR (NCT00578006), found that patients who self-reported symptoms had a higher rate of overall survival than those who reported symptoms the traditional way (P = .03). Another study, PRO-TECT (NCT03249090), was designed as a multicenter evaluation of the PROs method of ensuring good QOL. The trial was made up of 52 community oncology practices across 25 states, each enrolling up to 50 patients with metastatic cancer receiving systemic therapy who were not on a clinical trial.

During the study, patients were randomized 1:1 into either the intervention arm or a control arm. During the intervention arm, patients completed a weekly survey covering 12 common symptoms. An email alert was then sent to clinical nurses for severe or worsening symptoms so that they may be addressed. Reports showing longitudinal symptoms were sent to clinical teams at visits. In the control arm, patients received standard-of-care symptom management. End points of the study include survival, symptom control, health-related QOL, implementation, and satisfaction.

In the experimental arm (n = 593), median age of patients was 64 (range, 29-89) and 60.5% were women. Races of patients included White (80.4%), Black/African American (16.8%), and Asian American (2.1%). Cancer types observed included thoracic (19.9%), breast (16.4%), gastrointestinal (29.2%), genitourinary (11.6%), gynecologic (10.8%), hematologic (5.2%), and other (6.9%). Thirty-seven percent of patients had a high school education or less, 27.3% lived in a rural area, and 26.5% had never used an email or computer.

Among the 20,565 completed surveys, 33.9% triggered email alerts, most commonly for pain, diarrhea, dyspnea, and nausea. Nurses acted on 59.1% of these email alerts, mostly through telephone counseling, supportive medications, referrals, and new appointments. Eighty-three percent of patients strongly agreed that questions were easy to understand, 84% strongly agreed with the statement that the system was easy to use, and 70% would recommend the system to others. Seventy-two percent said that the system improved discussions with doctors or nurses, 70% felt that doctors or nurses used the information reported, and 78% reported that it made them feel more in control of their own care.

Seventy-eight percent of nurses felt the information was helpful for documentation. Additionally, 84% reported the information improved discussion with patients, and 84% reported the information improved efficiency. However, only 59% said they would recommend the system to future patients and only 64% said they would recommend the system to other clinics.
methods, and histology-based measures.

Treatment options, including chemotherapy and immunotherapy that are based on available molecular biomarkers, are incorporated into The National Comprehensive Cancer Network (NCCN) guidelines. More research is ongoing to assess the efficacy of treatments such as the RAINBO umbrella program, which evaluates biomarker-targeted treatments in 4 molecular subtypes: p53 abnormal, dMMR, POLE-mutated, and those subtypes with no specific molecular profile.

In an interview with Casey M. Cosgrove, MD, an assistant professor in the Department of Gynecologic Oncology at The Ohio State University College of Medicine in Columbus, discussed his presentation at the Society of Gynecologic Oncology (SGO) 2022 Winter Meeting about the current state of biomarkers for patients with endometrial cancer and how they can be used for prognostic and predictive purposes.

**Q:** What is the current landscape of endometrial cancer?

**A:** Endometrial cancer is one of the few cancers that is getting worse. We have more patients dying of endometrial cancer now than we did last year, and that’s a travesty. Endometrial cancer is aligning itself to overtake ovarian cancer as the deadliest gynecologic cancer in the United States.

We need our researchers and clinicians to be aligned with what patients [with] poor outcomes are seeing.

**Q:** Targeted Therapies in Oncology™ (TTO):
Please explain the interest in biomarkers for endometrial cancers.

**A:** COSGROVE: With many types of cancers, we’re starting to look at a more specialized approach [on] how we can better take care of our patients. Endometrial cancer certainly has many opportunities where we can identify molecular markers or things that we can’t see under the microscope to help guide the best way to treat patients.

We can use biomarkers to treat patients, to guide which trial metric to use, [or] which type of treatment we want to use. But we can also use biomarkers to tell us which patients should be treated or maybe should not be treated. It’s an incredibly exciting area of research for endometrial cancer because it allows us to home in on their individual types of cancers and treat them with the most individualized approach.
Q: What biomarkers are most relevant to endometrial cancer and what role do they play?
A: With biomarkers in endometrial cancer, there are 2 fundamental questions. The first question is, “Who should we be treating?” Several studies have looked at the ways that we can predict whether patients’ cancers will come back. [Traditionally], we’ve been guided by [cancer] stages or the histology, as well as several other features. But now we are starting to appreciate that we can use molecular signatures to tell us whether these cancers are at higher or lower risk for recurrence.

Reports from our group, as well as others have looked at different markers that have predicted higher-risk cancers. These can be things like p53 or genomic alterations and several other mutations we’ve noted. If we identify patients that have some of those higher-risk features, they may benefit from having extra treatment. There’s also a marker called POLE, which is needed to help the DNA repair itself. This allows for your body’s immune system, without any additional treatment, to fight those cancer cells better. We see that those patients [with POLE] tend to not [have their cancer] recur.

A question we’ve been asking has been, “Can we not treat these patients, even if they traditionally would have had higher-risk features?” The other major question that we’ve been trying to address with biomarkers is, “Can we work smarter, not necessarily harder? Can we target therapies that are based off molecular signatures?”

Perhaps the one that we have the most research and knowledge about and most experience with is deficiencies in MMR proteins or MSI within endometrial cancers. These markers predict response for immunotherapies. When we look at an endometrial cancer that has 1 of these markers, perhaps we should jump right to immunotherapy as opposed to going through our [traditional] chemotherapy algorithms. We also know that the MMR and MSI status can be an important prognostic biomarker because these patients seem to also have poor outcomes.

So taken together, a patient [with] a dMMR tumor or MSI-high tumor may benefit from having more aggressive treatment and a smarter treatment with immunotherapy as opposed to traditional chemotherapy.

Q: What are the most significant findings you’re presenting at the SGO Winter Meeting?
A: The most significant findings we’re presenting are the potential areas for improvement for patient care on the horizon. There are several ongoing clinical trials that are trying to refine the way we take care of a patient with endometrial cancer. What I hope we can see through all these clinical trials is that we have some easily applied clinical markers that are going to directly impact our decision-making. The ProMisE [Proactive Molecular Risk Classifier for Endometrial Cancer system] from the University of British Columbia, which establishes endometrial cancer into 4 molecular groups, has the most traction right now throughout the gynecologic oncology community. This is testing for dMMR, POLE [mutations], as well as p53 [positivity], and grouping endometrial cancers into 1 of 4 groups.

Depending on which group of [patients] fall into, the next question is, “What’s the best treatment for those individuals?” This has been evaluated through several trials right now. There’s a lot of excitement that hopefully we’ll be getting some answers in the next couple of years. I think the endometrial cancer [setting] has a lot of opportunity for growth in patient care. And [we] as clinicians are going to have to start integrating a lot of this information quickly as it becomes more available. With the improvements in technology, we’re going to be getting more information for each cancer type than we’ve ever had before. I can see assimilating that information into the clinical setting as a major barrier for patients and clinicians. But hopefully, we’ll have some standardized protocols that allow us to have the right way to take care of each patient.

Q: How do the NCCN guidelines align with the new biomarker research you are discussing?
A: Within the past 1 or 2 years, the NCCN guidelines have started incorporating the algorithms for molecular classification with endometrial cancer. Traditionally, we’ve broken endometrial cancers into type 1 and type 2, with type 1 being a less aggressive type and type 2 being more aggressive. What the Cancer Genome Atlas [TCGA] did in 2013 was to break endometrial cancer into 4 important groups with differing risk of recurrence and molecular features. Recent research has tried to integrate those in the clinical setting because TCGA uses technologies we can’t apply to the bedside. By utilizing newer technologies, we’re able to start integrating some of their findings into clinical care.

The NCCN has started to appreciate that and [uses] the algorithm for breaking endometrial cancers into 4 molecular groups as opposed to the 2 groups we had traditionally [used]. There’s also greater emphasis on what we can do with that information in the NCCN guidelines. For instance, one of the most important molecular groups is the MSI or dMMR group. Not only is this an important prognostic biomarker, but it’s also a predictive biomarker for the use of immunotherapy. That has been highlighted in the more recent editions of the NCCN guidelines, where they say if you have a recurrence with an MSI-high disease or dMMR, then immunotherapy is appropriate.

The other thing that the NCCN guidelines highlight is that even in the absence of having a biomarker, patients [can] get immunotherapy with the combination of lenvatinib [Lenvima] and pembrolizumab [Keytruda]. Sometimes having a negative biomarker can be just as informative for guiding treatment.

Q: Are there any other studies that are upcoming that you feel are important to biomarkers in the endometrial setting?
A: The RAINBO [set of trials] is very exciting because not only are they using the molecular classifications to determine the risk for recurrence and the aggressiveness of treatment, but they’re also integrating novel treatment strategies for the different molecular groups. I might identify that a patient is at higher risk, and I know what [treatments are] available, but I can [consider adding] more targeted therapies because of that molecular class, and I can treat them more aggressively and with a smarter therapy.

One of the things most notable from my presentation is the vast amount of ongoing research that we have in the area right now, which also highlights the number of unknown questions. One of the potential concerns we may have is that physicians may start integrating little pieces of this information into their clinical practice, without having a full tool belt available for what they need to be doing and what are the right tests and treatments that might be available.

Q: What is the most important takeaway that you would like community oncologists to get from your presentation?
A: We don’t have all the answers quite yet, and we’re still working on it. As we get...
more information, [we may find other biomarkers] to look for. It’s hard to cherry-pick 1 or 2 things that physicians can utilize [for all their patients]. The question is whether we need to have a whole grouping of testing to make the right decision for our patients.

We’re [now in] a situation where there are clearly defined biomarkers that can be utilized in a clinical setting, like dMMR or MSI status and increase in tumor mutational burden, but we still have unclear knowledge whether a patient with a tumor with [for instance] a POLE mutation can safely forego treatment. If you hear that these tumors have no recurrences, [we want to know] why we are treating them with chemotherapy and radiation, which have high toxicities, but at the same time we haven’t clearly proven that withholding treatment is not compromising outcomes.

Right now, physicians must continue to integrate the right biomarkers that we have information for into clinical practice. It’s easy to order a lot of testing, but if we don’t have a clear game plan with what we’re going to do with that testing, then we [could] harm our patients.

Some caution [must] be applied when we’re discussing biomarkers and new technologies with any cancer types. Another thing highlighted in our presentation is our reliance on our [traditional] pathologic findings, histology, and stage and how we integrate that into our patient care algorithms. Once we start getting more molecular data, how do we integrate the old and new data? What do we do if we don’t have conflicting information? It could cause problems in the future if we don’t adequately study these questions.

**REFERENCES**


It’s Time to Redefine Treatment

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What are some of the disease-specific challenges of developing novel therapies for patients with cervical cancer?

Cervical cancer is a unique disease and patient population for us compared with endometrial and ovarian cancer. Metastatic and recurrent cervical cancer is not as common in our practice. [Cervical cancer] is not a very common disease overall, so that’s one challenge. One of the unique things about patients with cervical cancer is that they’re quite young overall. [Women with cervical cancer] are very young, otherwise healthy women, sometimes with families and children. It’s an important population, even though it’s a smaller population to focus on. The other thing that is important to highlight is that cervical cancer and advanced cervical cancer...is an even bigger problem worldwide in underdeveloped countries or countries where preventive care is less robust. A lot of the breakthroughs that we have in the United States may not be as applicable globally. It is a very niche type of research that’s done with these advancements, because it’s a smaller population with needs that vary from country to country. The population is very heterogeneous too, even in the United States.

What therapeutic class has the most potential to make an impact on the treatment paradigm?

With immunotherapy and immunotherapy combinations—not just pembrolizumab-based combinations, but other immunotherapy combinations and novel immunotherapy agents, such as...[tumor-infiltrating lymphocyte] treatment—there is a growing amount of knowledge in the role of the immune system and the potential hope we have in immunotherapy, not just as single agents but also in combination with standard regimens. I don’t think that the future of cervical cancer is going to be...on giving 1 drug at a time. I think the future of cervical cancer treatment is going to be using combinations of multiple treatments to see improvement in survival.

What can be done to make sure that these developments reach the community at large?

There are significant disparities in our country’s health care system. [Patients with cervical cancer] have a vast demographic makeup with many cultural and racial ethnic backgrounds. By allowing and supporting clinical trial enrollment for every [individual] and population, we hope to improve the extension of these novel therapies to populations or subsets that normally wouldn’t have had access to them. There certainly is a lot of work to do to reach out to patients who are under[insured] or noninsured and patients who don’t have access to larger or tertiary medical centers with novel therapies available.

Is there any research you’re involved in that you’d like to highlight?

So much activity is going on now in cervical cancer trials across the country, including the addition of immunotherapy to the chemoradiation backbone for locally advanced disease and looking at combinations of therapies. Now that patients are getting immunotherapy in the first-line setting, [we are asking,] what do we do with immunotherapy if they progress and need something in the second-line setting? Should patients get immunotherapy again? Should we switch classes? How do we make immunotherapy effective and tolerable at the same time?

The trial that I’m involved in in the cervical cancer field is looking at adding triapine, which is a novel drug, to the backbone of chemotherapy and radiation in locally advanced cervical cancer.
surgery at Banner MD Anderson Cancer Center in Gilbert, Arizona. For localized disease, the use of ctDNA for both quantitative and qualitative detection can inform the risk of recurrence and metastatic dissemination. In CRC, ctDNA has been thoroughly studied.²

“I’m fortunate to be delivering the plenary session,” Choti said in an interview with Targeted Therapies in Oncology. “It’s exciting because this is going to be a transformative tool…” He noted that the use of ctDNA is selective, with some aspects covered by insurance and others that are more limited. ctDNA allows for a greater understanding of the tumor’s molecular genetics; its advantage over biopsy is that it can be used to determine the full genomic profile of a patient with cancer.

Another evolving use of ctDNA is for monitoring a particular treatment. For example, if a patient with advanced disease is being treated with chemotherapy, the traditional way to measure response is to have the patient undergo scans a month or 2 after delivery of the drug. If ctDNA is being used for monitoring, the oncologist can see a difference in tumor burden, sometimes even 1 day or a week later, noted Choti. “It gives the physician the ability to nimbly adjust therapy to determine if that therapy is working,” he said. The advantage is that the patient is not subjected to treatments that are not working or to extensive adverse events.

From a longitudinal standpoint, ctDNA can inform clinicians about changes in the clonal composition of tumor tissue over time, which can lead to further stratification of treatment. Performing liquid biopsies that isolate and analyze ctDNA at different time points can alert the clinician to heterogeneous changes during treatment. Based on this concept, more precise therapeutic schedules can be formulated for patients with cancer in different stages.³

Choti cautioned that although this is exciting, “what’s needed is to get the word out in the community so that clinical trials can be designed and enrollment can begin that will [eventually] validate the concept.”

The overall goal of the conference emphasizes the multidisciplinary care that is required for patients with gastrointestinal (GI) cancers. Choti and his co-chair, John L. Marshall, MD, chief, Division of Hematology/Oncology at Medstar Georgetown University Hospital; professor of medicine and oncology, Lombardi Comprehensive Cancer Center at Georgetown University; and director, Ruesch Center for the Cure of Gastrointestinal Cancer, structured the conference to highlight practical application of knowledge to the complex care scenarios encountered in practice settings, rather than taking an esoteric approach.

Medical Crossfire

In addition to the plenary session, Choti also emphasized the Medical Crossfire session, which will explore the role of immunotherapy in GI cancer. Early immunotherapy experience in GI cancers was not well received, with negative findings from trials and minimal advancements. But that has changed with the incorporation of immune checkpoint inhibitors in upper GI cancers.

For example, the FDA approved nivolumab (Opdivo) in combination with chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.⁴ In the randomized, multicenter, open-label CheckMate 649 trial (NCT02872110), investigators enrolled 1581 patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma.
Findings demonstrated a statistically significant improvement in progression-free survival (PFS) and overall survival (OS) for patients with PD-L1 with a combined positive score (CPS) of 5 or greater.

Median OS was 14.4 months (95% CI, 13.1-16.2) in the nivolumab plus chemotherapy arm vs 11.1 months (95% CI, 10.0-12.1) in the chemotherapy alone arm (HR, 0.71; 95% CI, 0.61-0.83; \( P < .0001 \)).

Median PFS was 7.7 months (95% CI, 7.0-9.2) in the nivolumab plus chemotherapy arm vs 6.0 months (95% CI, 5.6-6.9) in the chemotherapy alone arm (HR, 0.68; 95% CI, 0.58-0.79; \( P < .0001 \)).

Longer follow-up data confirmed nivolumab plus chemotherapy as a new standard first-line regimen.\(^5\)

**Tumor Board**

A tumor board featuring real cases will be co-chaired by Choti and Marshall. Participants can look forward to a lively interaction that will foster the exchange of ideas, best practices, and collaboration. TT

**REFERENCES**

Evolving Biomarkers Span Proteomic, Genomic Fields in Multiple Myeloma

By Thao K. Adams, PharmD, BCOP

Several next-generation biomarkers are currently emerging in multiple myeloma (MM) that could lead to improved clinical management and outcomes, as well as enhanced precision medicine. “There are still a lot of things that are ongoing, and the myeloma field is evolving with new treatments. It’s a very interesting time for myeloma research in general and for patients with myeloma. There is a lot of interest to understand the disease better,” said Mark Bustoros, MBBCh, assistant professor of medicine at Weill Cornell Medicine, Cornell University, and the Division of Hematology and Medical Oncology at NewYork-Presbyterian Weill Cornell Medical Center.

MM is a hematologic malignancy characterized by proliferation of abnormal plasma cells in the bone marrow. Diagnosis and risk stratification of MM depend on primary biomarkers, M protein, β2-microglobulin, albumin, and lactate dehydrogenase.1 Biomarker assessment is performed using electrophoresis, fluorescence in situ hybridization (FISH), and imaging to diagnose and risk-stratify the disease.2

Biomarkers in MM also contribute to determining the stage of the disease in patients. The International Staging System (ISS) and, most recently, the Revised International Staging System (R-ISS) are used to stage patients.3 The R-ISS incorporates cytogenetic abnormalities, signifying the importance of the involvement of genomics in the prognosis of patients.1-3

Discussing the current staging system in the era of novel treatment options in MM, Bustoros said that “with the advent of the new therapies—especially the monoclonal antibodies such as daratumumab [Darzalex], chimeric antigen receptor [CAR] T, and other immunotherapies—[the relationship between the staging system and novel treatments] is in flux.”

Although there are established biomarkers for MM, novel biomarkers are needed for improved disease diagnosis and treatment.4 The complexity of the disease, along with novel treatment approaches, warrants the exploration of unique biomarkers for improving early diagnosis and optimizing response to treatment, which may lead to improved clinical management of MM and survival outcomes.

Minimal residual disease (MRD) is being assessed in clinical practice and has emerged as a pertinent and potential surrogate biomarker in MM.2 Patients who achieve MRD-negative status have longer progression-free survival (PFS) and overall survival (OS); therefore, MRD is a useful prognostic tool.2

“We’re looking at MRD assessment in the marrow, based on sequencing of the immunoglobulin light and heavy chain genes from the malignant plasma cells at diagnosis, which are unique sequences, similar to a fingerprint…[this] serves as a really good predictor of long-term response in myeloma. I’ve been routinely sending MRD assessment on patients [who have just received diagnoses] for several years because the test is now authorized by the FDA,” said Thomas G. Martin, MD, clinical professor of medicine, associate director of the Myeloma Program at University of California San Francisco, and coleader of the Cancer Immunology & Immunotherapy Program at Helen Diller Family Comprehensive Cancer Center, also in San Francisco.

“We’re entering the immunotherapy era for treating relapsed [MM] and these novel drugs, most targeting B-cell maturation antigen (BCMA), are showing impressive early results,” Martin said. The high-specific and tissue-specific expression of BCMA on myeloma cells has quickly advanced this target and propelled the development of novel BCMA-directed therapies in myeloma.4 Additional evidence has demonstrated that soluble BCMA (sBCMA) levels may be a useful biomarker for precursor plasma cell disorders including monoclonal gammopathy of undetermined significance and smoldering MM. In a retrospective study, increased levels of sBCMA in the precursor state were associated with disease progression to active MM. Additionally, patients with higher baseline sBCMA levels had poorer PFS and OS outcomes.4

Martin added, “The hard part about soluble BCMA is that there’s not a currently available CLIA [Clinical Laboratory Improvement Amendment] test. Studies are evaluating whether sBCMA can accurately predict response to therapy and may be an early marker for recurrence/progression. So far, several studies have shown that when a patient has...”

CONTINUED ON PAGE 53 ?>
INDICATION
TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

IMPORTANT SAFETY INFORMATION
BOXED WARNING: NEUTROPENIA AND DIARRHEA
• Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.
• Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.

CONTRAINDICATIONS
• Severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS
Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.
Diarrhea: Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 diarrhea.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions.


For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease.

A WAY IN WITH TRODELVY
TRODELVY attacks mTNBC with an antibody-drug conjugate (ADC) that binds to Trop-2.

Based on preclinical data. May not correlate with clinical outcomes.
For adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

**TRODELVY IMPROVED SURVIVAL IN 2L+ mTNBC**

*In the phase 3 ASCENT trial*

**PROVEN SURVIVAL BENEFIT**

<table>
<thead>
<tr>
<th>In brain metastases-negative (BM-neg) population*</th>
<th><strong>3X LONGER MEDIAN PFS</strong> than single-agent chemotherapy</th>
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<tbody>
<tr>
<td><strong>5.6 months</strong> with TRODELVY (range: 4.3–6.3) (n=233) vs 1.7 months with single-agent chemotherapy (range: 1.5–2.6) (n=233); 95% CI, HR: 0.41 (0.32–0.52) P&lt;.0001</td>
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In the full population**

- Median PFS was 4.8 months for TRODELVY (range: 4.1–5.8) (n=267) vs 1.7 months with single-agent chemotherapy (range: 1.5–2.5) (n=262); 95% CI, HR: 0.43 (0.35–0.54) P<.0001

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<tr>
<th>In BM-neg population**</th>
<th><strong>1 YEAR MEDIAN OS</strong></th>
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<td><strong>12.1 months</strong> with TRODELVY (range: 10.7–14.0) (n=233) vs 6.7 months with single-agent chemotherapy (range: 5.8–7.7) (n=233); 95% CI, HR: 0.48 (0.38–0.59) P&lt;.0001</td>
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In the full population**

- Median OS was 11.8 months for TRODELVY (range: 10.5–13.8) (n=267) vs 6.9 months with single-agent chemotherapy (range: 5.9–7.6) (n=262); 95% CI, HR: 0.51 (0.41–0.62) P<.0001

*TRODELVY was studied in ASCENT, a phase 3, randomized, active-controlled, open-label trial. Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=267) or physician's choice of single-agent chemotherapy (n=262), which included eribulin, vinorelbine, gemcitabine, or capecitabine. Patients were treated until disease progression or unacceptable toxicity. The efficacy analysis included Progression-Free Survival (PFS) in BM-neg patients (primary endpoint) by BICR based on RECIST 1.1 criteria. PFS for the full population (all patients with and without brain metastases), and Overall Survival (OS) vs single-agent chemotherapy.

- 88% of the full population were BM-neg.1 Results in these patients were similar to those seen in the full population (all randomized patients).2
- See exploratory findings for BM-positive population at TRODELVYHCP.com

- 13% of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy). Efficacy results for this subgroup of patients were consistent with those who had received at least 2 prior lines in the metastatic setting1

BICR=blinded, independent, central review; CI=confidence interval; HR=hazard ratio; OS=Overall Survival; PFS=Progression-Free Survival; RECIST=Response Evaluation Criteria in Solid Tumors.

emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

**Nausea and Vomiting:** Nausea occurred in 66% of all patients treated with TRODELVY and Grade 3 nausea occurred in 4% of these patients. Vomiting occurred in 39% of patients and Grade 3-4 vomiting occurred in 3% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV). Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to Grade 1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

**Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity:** Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of Grade 3-4 neutropenia was 67% in patients homozygous for the UGT1A1*28, 46% in patients heterozygous for the UGT1A1*28 allele and 46% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 function.

**Embryo-Fetal Toxicity:** Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. 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 TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

**ADVERSE REACTIONS**

In the ASCENT study (IMMU-132-05), the most common adverse reactions (incidence ≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

**DRUG INTERACTIONS**

**UGT1A1 Inhibitors:** Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.


Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.
BOXED WARNING

Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below

3,000/mm3 for neutropenia and monitor blood counts, especially during lymphocyte depletion. Consider prophylactic antibiotics. Initiate anti-infusion treatment in patients with febrile neutropenia without delay.

Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the coding diphosphate-glycuronosyltransferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of neutropenia and anaemia was analyzed in patients who received TRODELVY. The incidence of Grade 3 neutropenia was 67% in patients homozygous for the UGT1A1*28 allele (n=87), 46% in patients homozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=831). The incidence of Grade 3 anaemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 1% for patients homozygous for the wild-type allele. Close monitoring patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

Emesis-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a teratogenic component, 3,4- and 3,5-estradiol diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of neutropenia and anaemia was analyzed in patients who received TRODELVY. The incidence of Grade 3 neutropenia was 67% in patients homozygous for the UGT1A1*28 allele (n=87), 46% in patients homozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=831). The incidence of Grade 3 anaemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 1% for patients homozygous for the wild-type allele. Close monitoring patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

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use include proteomic and angiogenesis biomarkers. The use of proteomic biomarkers has the potential to provide diagnostic and prognostic information in patients with MM. Further research into proteins such as proteasome activator complex subunit I, heat shock protein 90, and others may provide insight into how these proteins may be used as biomarkers for patients with MM in the future. Angiogenesis biomarkers are known to be associated with tumor cells requiring adequate blood supply for tumor growth. Markers associated with angiogenesis may include VEGF, hepatocyte growth factor (HGF), angiopoietins, and JUNB.

There don’t seem to be [many] mutations that are targetable in myeloma. We do see KRAS, NRAS, and occasional BRAF mutations, so we do see mutations in which there may be drugs that potentially could target these pathways, but there are only a few studies investigating specific mutation-driven treatment in patients with myeloma. We’re really at the infancy compared with other malignancies such as lung cancer,” said Martin.

“Progress continues in the research and development of biomarker assessment in MM. The complexity of the disease may warrant multiple biomarkers to provide clarity on diagnosis, prognosis, and response to treatment with the goal of personalizing patient treatment to improve outcomes.

“There are a lot of evolving biomarkers and that will benefit patient treatment…integrating genetic biomarkers with biomarkers that can be measured from blood samples, bone marrow biopsies, and circulating tumor cells,” Bustoros said. “All of this would be used in the future to identify patients who would progress at very early time points. I think biomarkers would be very important to tailor therapy for specific patients…the sequence of treatment also would benefit from understanding the biomarkers and knowing the biomarkers of response.”


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a great response, the sBCMA levels become undetectable and when sBCMA levels become detectable, it’s a sign that the myeloma is growing back again. We are very hopeful that a CLIA test will be developed and that sBCMA will be an excellent biomarker for [MM].”

Another potential novel biomarker is the presence of the translocation t(11;14) by bone marrow FISH testing.3 “The t(11;14) translocation in myeloma is associated with the upregulation of BCL2 pathway, and thus researchers began investigating the clinical use of BCL2 inhibitors in this subset of patients,” said Martin. Patients whose myeloma cells express the t(11;14) translocation have demonstrated clinical responses to venetoclax (Venclexa).

According to Bustoros, “Until now, the only known predictive biomarker for response to therapy in a patient is having t(11;14). We know venetoclax would be a good option for [patients with t(11;14)] at relapse. It’s not [FDA] approved for up-front treatment yet.”

Looking into the future for using t(11;14) as a biomarker for drug therapy, Martin added, “There are trials going on right now using venetoclax in patients with t(11;14) and those patients do extremely well…I suspect [venetoclax] will be approved for use in patients with t(11;14) as part of frontline therapy and in relapse within the next few years.” Other exploratory biomarkers that may be associated with t(11;14) are del(17p) or gain(1q).3

Other emerging biomarkers include circulating tumor cells (CTCs) and microRNAs (miRNAs). “[miRNAs] and CTCs are in early investigations in myeloma and we’re still figuring out which assays to use, and how and in which patients these bioassays may help,” said Martin. CTCs were found to be released in the peripheral blood of MM from the tumor cells in bone marrow and detected by flow cytometry.1,2

The benefit of CTCs is the noninvasive nature of their use for detecting MM compared with a bone marrow biopsy for diagnosis.3 Additionally, the use of CTCs may be prognostic at diagnosis and they may be used in conjunction with MRD as a response biomarker.1

miRNAs are expressed on all cells and consist of short noncoding RNAs. MiRNAs are an attractive biomarker in MM due to their function as tumor promoters or suppressors. There is potential for the use of miRNAs in the diagnosis and prognosis of MM. However, more research is needed for validation of miRNA use. “Given the difficulties in isolating [miRNAs], detecting them, and measuring them, I would say it needs time to be translated clinically,” said Bustoros.

Other novel biomarkers that may warrant further exploration and evidence for
Hepatocellular Carcinoma: A Decade of Treatment Advances
By Benjamin Holmes, DVM

In CONJUNCTION WITH the 10-year anniversary of Targeted Therapies in Oncology®, we are highlighting the most impactful advancements in the treatment of hepatocellular carcinoma (HCC) during the previous decade.

Three experts offered their thoughts and insight about the past 10 years of research and treatment of this disease: Tanios S. Bekaii-Saab, MD, FACP, medical director of the Cancer Clinical Research Office and vice chair and section chief for medical oncology in the Department of Internal Medicine at Mayo Clinic; Richard S. Finn, MD, a professor of medicine and director of the Translational Research Laboratory in the Division of Hematology/Oncology at UCLA Jonsson Comprehensive Cancer Center at David Geffen School of Medicine at UCLA; and William P. Harris, MD, associate professor in the Division of Oncology at the University of Washington School of Medicine.

Etiology/Pathogenesis
Improved understanding of the pathogenesis of a disease and the development of effective treatments generally result in a decrease in the incidence and mortality rates of cancer. Despite advancements in the field of HCC, incidence and mortality rates are continuing to increase globally.1 Within the United States, incidence rates increased during the first half of the decade but have begun to slightly decrease, and mortality rates have remained fairly steady.2

The highest historical risk factors for developing HCC have been hepatitis B virus (HBV) and hepatitis C virus (HCV).2 Since 2014, several antiviral options for HCV have been approved, resulting in higher rates of sustained virological response (SVR).4 SVR has been associated with a considerable decreased risk of HCC, although the risk is still present for patients with HCV and cirrhosis. Proper vaccination programs and availability of HBV vaccines have greatly decreased incidence in countries such as the United States, but HBV remains a global concern, especially in Asia.5

With the widespread use of vaccines for HBV and the availability of antivirals for HCV, Bekaii-Saab noted that countries such as the United States could experience a drop in the incidence of HCC. “The primary driver was viral hepatitis; however, the pathogenesis of HCC is shifting and continues to shift,” Bekaii-Saab said. “More and more, due to the incidence of increased obesity and nonalcoholic fatty liver disease [NAFLD], NASH [nonalcoholic steatohepatitis] is becoming the driver.” NASH and NAFLD are significantly contributing to the current number of HCC cases and are predicted to result in continually increasing incidence rates.6

NASH and NAFLD are related to obesity and type 2 diabetes mellitus, which can be driven by both environmental and genetic factors.6 The projected prevalence of NAFLD by 2030 is 33.5%, inevitably resulting in increased mortality rates.7 Harris hopes we can prevent future HCC by targeting at-risk patients for hepatic disease.

“We need to do a better job recognizing high-risk patients. Treatment of hepatitis, obesity, and diabetes can decrease the risk of NASH and HCC,” Finn said, adding that he sees NASH as the next hurdle to overcome. “Incidence from hepatitis C is expected to decline, but NASH is a very potent risk factor for many patients and is becoming the next battle in the primary space.”

Diagnosis/Surveillance
Imaging provides a noninvasive approach to diagnosis, staging, and follow-up, and in recent years, the approach to imaging in HCC has shifted from a qualitative to a more quantitative approach.8 The quantitative approach is an attempt to use imaging parameters such as spatial differences in brightness to help create a reproducible signature that accurately represents the given pathophysiology.

To assist in standardizing the approach to HCC diagnosis and improve communication between clinicians, the Liver Imaging Reporting and Data System (LI-RADS) was developed. LI-RADS continues to be updated, integrating various modalities (CT, MRI, contrast-enhancing ultrasound) and conforming to the American Association for the Study of Liver Diseases disease recommendations.9,10

“The main changes for diagnostic imaging [have] been in the standardization of reporting with the LI-RADS system,” Harris said. “This is becoming a standardized mechanism to determine which lesions appear definitive for liver cancer.
radiographically and has begun to incorporate parameters on treatment response.”

Although the standardization of imaging technique and assessment through LI-RADS certainly increases the likelihood of a proper diagnosis, it still lacks the desired sensitivity and specificity. Up to 38% of LI-RADS 3 classifications (intermediate probability of malignancy) and 13% of LI-RADS 2 classifications (probably benign) are confirmed as HCC by pathological diagnosis.2

Investigators continue to work toward improved MRI and CT techniques to better assess preoperative parameters, such as microvascular invasion and liver status and portal hypertension. Numerous approaches have also been developed— and are continuing to be developed—to aid with prognosis and proper assessment of treatment response. Currently, there is no standardized approach, and no imaging study has been able to accurately determine histologic subtypes of HCC.3

Finn appreciates the advancements but points out that more education is needed for community oncologists. “If you’re in the liver cancer space you understand the LI-RADS, but many in the community won’t,” he said. “There’s still a lot of education needed to understand how to follow patients with liver cancer—how to assess response.”

Bekaii-Saab admits the screening process is important but requires further optimization and has concerns about access issues for at-risk population groups within the United States. “Current imaging screening is still important, and picks up patients in earlier stages, but we’re not where we want to be yet. There is also an access issue in the United States. We should be focusing on patients with higher risk, but we see a lot of liver disease in patients with decreased access, such as Hispanics and Native Americans.”

**Locoregional Treatment**

Transarterial chemoembolization (TACE) remains the standard-of-care treatment for patients with intermediate-stage HCC.2 However, the recent development of transarterial radioembolization (TARE) could potentially change that in the future.25 TARE spares healthy liver parenchyma by delivering high-dose beta radiation to the capillary bed of the tumor. A catheter is used to administer glass or resin microspheres embedded with yttrium 90–emitting beta radiation. Current data suggest TARE is an effective option for liver-limited, unresectable disease.21,24 Data from a meta-analysis suggest that TARE is not as effective as TACE or as TACE with drug-eluting beads in terms of overall survival (OS), but that TARE produces significantly fewer complications.13 Further studies are needed before TARE could possibly replace TACE, but many clinicians already prefer TARE to TACE for its tolerability.

Harris mentioned that despite not many additional locoregional approaches, the available modalities are continuing to improve and become more precise. “Local interventions have developed over the past 10 years with the understanding that we want to be more selective in our treatments while sparing healthy liver parenchyma,” he said.

“Localized interventions will continue to be honed. Promising outcomes are currently achieved for treating single tumors up to 8 cm in size with or without focal vascular invasion with high-dose ablative radioembolization administered selectively. We see response rates pushing 90% with durable responses.”

**Systemic Treatments**

The greatest advancements in HCC during the previous decade have been the number of systemic therapeutic approvals (**Figure**). The multikinase inhibitor sorafenib (Nexavar) was approved as first-line therapy for HCC in 2008 based on results of the SHARP trial (NCT00105443).22 “Sorafenib improved survival but didn’t have a large impact on objective response rate, continuing our reliance on interventional techniques,” Finn said.

Bekaii-Saab added, “It’s an incredibly tough drug to use, but it was a welcome option, as there was nothing else available.”

Many thought sorafenib would quickly lead to further drug developments and approvals, but there was a drought of negative trials that occurred during the next decade. The next drug approval wasn’t until 2017—and that did lead to a flood of new approved drugs for HCC.

**Regorafenib**

The multikinase inhibitor regorafenib (Stivarga) targets VEGFR1/2/3, among other kinases. This was the first second-line therapy approved,22 it is indicated for the treatment of patients who progressed on sorafenib. Data from the registrational

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**Figure. Timeline of Systemic Therapy Approvals in HCC**

<table>
<thead>
<tr>
<th>Date</th>
<th>Approval Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 19, 2008</td>
<td>FDA approval of sorafenib (Nexavar) for treatment of patients with unresectable HCC</td>
</tr>
<tr>
<td>April 27, 2017</td>
<td>FDA approval of regorafenib (Stivarga) for treatment of patients with HCC previously treated with sorafenib</td>
</tr>
<tr>
<td>November 9, 2018</td>
<td>FDA accelerated approval of ramucirubin (Keytruda) for patients with HCC previously treated with sorafenib</td>
</tr>
<tr>
<td>May 10, 2019</td>
<td>FDA approval of atezolizumab (Tecentriq) and bevacizumab (Avastin) in patients with unresectable or metastatic HCC without prior systemic therapy</td>
</tr>
<tr>
<td>September 22, 2017</td>
<td>FDA accelerated approval of nilotinib (Opdivo) for patients with HCC previously treated with sorafenib</td>
</tr>
<tr>
<td>August 16, 2018</td>
<td>FDA approval of lenvatinib capsules (Lenvima) for first-line treatment of patients with unresectable HCC</td>
</tr>
<tr>
<td>January 14, 2019</td>
<td>FDA approval of cabozantinib (Cabometyx) for treatment of patients with HCC previously treated with sorafenib</td>
</tr>
<tr>
<td>May 10, 2020</td>
<td>FDA accelerated approval of nivolumab (Opdivo) and ipilimumab (Yervoy) for patients with HCC previously treated with sorafenib</td>
</tr>
</tbody>
</table>

HCC, hepatocellular carcinoma.
HEPATOCELLULAR CARCINOMA

and a median OS of 12.9 months in patients
was approved in HCC based on results from the
Pembrolizumab (Keytruda), a PD-1 inhibitor,
became the preferred agent for many.

noninferior study doesn’t technically show
with grade 3 or higher drug-related AEs occur-
was decreased by 21% with pembrolizumab
plus best supportive care. The risk of death
zumab plus best supportive care vs placebo
a median OS compared with sorafenib (13.6 vs 12.3
months, respectively; HR, 0.92; 95% CI, 0.79-
1.06). It also achieved a significantly improved
PFS and ORR. However, lenvatinib’s rate of
treatment arms.23

Pembrolizumab

Pembrolizumab (Keytruda), a PD-1 inhibitor,
was approved in HCC based on results from the
phase 2 KEYNOTE-224 trial (NCT02702441),
which demonstrated a durable ORR of 17% and a
median OS of 12.9 months in patients
previously treated with sorafenib. However,
the follow-up phase 3 study, KEYNOTE-240
(NCT02702401), missed the pre-specified
P value required for statistical significance,
with a median OS of 13.9 months for pembrolizumab
vs 10.6 months for placebo (P = .02) and a median PFS of 3.0 months vs
2.8 months, respectively (P = .018).20

In 2021, the FDA’s Oncologic Drugs Advisory
Committee discussed the pembrolizumab
HCC indication, among others, and unanimously
voted in favor of continued approval.21

Data presented at the 2022 Gastrointesti-
nal Cancers Symposium from the phase 3
KEYNOTE-394 trial (NCT03062338) indicate a
significant improvement in OS for pembroli-
zumab plus best supportive care vs placebo
plus best supportive care. The risk of death
was decreased by 21% with pembrolizumab
(HR, 0.79; 95% CI, 0.63-0.99; P = .0180), with a
median OS of 14.6 months vs 13.0 months
for placebo.22 This will likely keep pembroli-
zumab as a second-line monotherapy option
despite the KEYNOTE-240 results.

Cabozantinib

Cabozantinib (Cabometyx), another multi-
kinase inhibitor, received approval based on
findings from the CELESTIAL trial
(NCT01908426), which showed a median OS
of 10.2 months for cabozantinib compared
with 8 months for placebo (HR, 0.76; 95% CI,
0.63-0.92; P = .0049). The median PFS was 5.2
months with cabozantinib and 1.9 months
with placebo (HR, 0.44; 95% CI, 0.36-0.52;
P < .001). ORRs were less than 10% in both
treatment arms.23

Ramucirumab

Ramucirumab (Cyramza) is a VEGFR antago-
nist and the only biomarker-guided therapy for
HCC, requiring a baseline a-fetoprotein level of
400 ng/mL or more. In the phase 3 REACH-2
trial (NCT02434333), ramucirumab produced
an OS of 8.5 months vs 7.3 months for placebo
(HR, 0.710; 95% CI, 0.53-0.949; P = .0199) in
previously treated patients with HCC.

Nivolumab and Ipilimumab

Nivolumab (Opdivo) was initially approved as
a second-line monotherapy treatment based on
results of a portion of the phase 1/2 Check-
Mate 040 study (NCT01658878).24 In the phase,
nivolumab monotherapy induced an ORR
of 20%. However, the confirmatory phase 3 Check-
Mate 459 trial (NCT02576509) did not show a
statistically significant improvement in OS for
nivolumab compared with sorafenib (median
OS, 16.4 months vs 14.7 months, respectively;
HR, 0.85; 95% CI, 0.72-1.02; P = .075), resulting in
the withdrawal of the indication.25,26

The combination of nivolumab (an anti-PD-1
inhibitor) and ipilimumab (Yervoy; a CTLA-4
monoclonal antibody) was also explored in
the CheckMate 040 trial. An ORR of 32% and
a median OS of 22.8 months was achieved
in the nivolumab plus ipilimumab group.27
Based on these results, the FDA granted accel-
erated approval to the combination despite
immune-related toxicities that required
systemic corticosteroid use in 51% of cases.
Phase 3 trials are ongoing comparing this
combination with sorafenib or lenvatinib.3

Atezolizumab and Bevacizumab

The most important approval and overall
advancement in the treatment of HCC was
for the anti-PD-L1 antibody atezolizumab
(Tecentriq) with the anti-VEGF antibody beva-
cizumab (Avastin). This combination is the
first regimen to significantly improve OS vs
sorafenib in the frontline setting.28,29

IMbrave150 (NCT03434379) was an open-
label, randomized phase 3 trial compar-
ing the combination of atezolizumab and
bevacizumab with sorafenib as first-line
therapy for advanced HCC. An updated analy-
sis indicated a median OS of 19.2 months for
the combination arm and 13.4 months for
sorafenib monotherapy (HR, 0.66; 95% CI, 0.52-
0.85; P = .0009), along with a median PFS of
6.8 months for the combination arm vs
4.3 months for sorafenib (HR, 0.59; 95% CI,
0.47-0.76; P < .001). The ORR was 30% in the
combination arm, with a duration of response
of 18.1 months, vs 11% for sorafenib, with a
duration of response of 16.3 months.30

This approval shifted the preferred first-
treatment from sorafenib to atezolizumab
with bevacizumab. “Atezolizumab and beva-
cizumab showed significant improvement
compared to sorafenib along with improved
quality of life. This truly saved immuno-onco-
logy therapy by becoming the standard for
patients with HCC,” Bekaii-Saab said.

Looking Ahead

Harris, Finn, and Bekaii-Saab all agree that
further studies in second-line therapy after
immuno-oncology therapeutics, biomark-
ers for diagnosis and treatment selection,
and personalized therapies require more
investigation in the years to come. Several
studies have their attention, including the
phase 3 LEAP-002 study (NCT03713593)
evaluating lenvatinib plus pembrolizumab
for first-line treatment of patients with
advanced HCC. Recent outcomes from the
COSMIC-312 trial (NCT03755791) evalu-
ating the combination of cabozantinib
and atezolizumab vs sorafenib for first-line
therapy are encouraging, although not as
robust as results observed with atezolizum-
ab with bevacizumab. The HIMALAYA
trial (NCT03298451) recently found that the
anti-PD-1 antibody durvalumab (Imfinzi)
is noninferior vs sorafenib and produces
a meaningful OS benefit when given with
a high priming dose of tremelimumab (an
anti-CTLA-4 antibody) as frontline therapy
in patients with unresectable HCC.31

Although these preliminary results and
study designs are encouraging, the signifi-
cance of their impact is questionable. These
new treatments will provide options, but the
data are similar or even less robust com-
pared with the options already available. “In
my opinion, we need new strategies outside
of exploring our current options and how to
sequence them,” Harris said.

Finn concluded, “We’ve seen significant
gains in overall survival, and that’s very
exciting coming from a decade where we were
improving survival but with stable disease.
Now we’re actually seeing tumors shrink.”
In November 2021, the European Society for Medical Oncology (ESMO) updated their clinical guidelines for the diagnosis and treatment of urothelial carcinoma (UC) to accommodate recent advances in therapeutic options.

ESMO Guidelines Primer

Much has changed in the understanding and treatment of UC, including the development and availability of pembrolizumab (Keytruda) and nivolumab (Opdivo) for UC, atezolizumab (Tecentriq) for advanced or metastatic UC, and the antibody-drug conjugate enfortumab vedotin-ejfv (Padcev),1 indicated for adult patients with locally advanced or metastatic UC (mUC). The strength of recommendation is guided by the supporting data (FIGURE2) and is in brackets at the end of the sentence to which it pertains.

Joaquim Bellmunt, MD, PhD, director of the Bladder Cancer Program at Beth Israel Deaconess Medical Center and associate professor of medicine at Harvard Medical School in Boston, Massachusetts, and one of the lead authors of the guidelines addressed the overall changes.

Treatment of Non–Muscle-Invasive Bladder Cancer

Complete removal of all visible lesions in the bladder via transurethral resection of the bladder tumor (TURBT) followed by intravesical instillation remains the optimal treatment of non–muscle-invasive bladder cancer (NMIBC) [I, A]. Patients with very high-risk disease should be considered for early radical cystectomy [RC; I, A]. The 2021 updated guidelines provide further detailed recommendations for low-, intermediate-, and high-risk NMIBC.2

BCG Failure

The updated guidelines contain recommendations for patients who experience failure on intravesical BCG therapy for intermediate- and high-risk disease. “Including information on BCG in the way that has been adapted by other urological guidelines is important because bladder cancer needs to be approached in a multidisciplinary way,” Bellmunt said in an interview with Targeted Therapies in Oncology™.

BCG failure is further broken down into 4 categories to properly identify patients who will no longer benefit from BCG therapy:3

1. BCG refractory—persistent high-grade (HG) disease at 6 months after adequate BCG treatment or T1/Ta HG at 3 months or stage progression at 3 months after proper BCG induction.
2. BCG relapsing—HG disease recurrence after achieving disease-free status within 12 months of adequate BCG
3. BCG intolerant—toxicity prevents the patient from receiving adequate BCG
4. BCG unresponsive—a combination of BCG-refractory and BCG-relapsing within 6 months of the last BCG.

For HG tumors unresponsive to BCG, RC should be pursued [III,B]. Thermochemotherapy and BCG reinduction are options only for patients unwilling or unable to pursue radiotherapy.4

According to investigators, thermochemotherapy has been shown to achieve a 47% 2-year disease-free survival (DFS) rate, although BCG reinduction achieved similar disease control in a randomized trial [II, B].5,6
A newly included option for BCG-unresponsive patients who are unable or refuse to pursue RC is the use of pembrolizumab [III, C].

The single-arm phase 2 KEYNOTE-057 trial (NCT02625961) showed a complete response (CR) rate of 41% (95% CI, 30.7%-51.1%) in 96 patients with BCG-unresponsive carcinoma in situ receiving intravesical pembrolizumab.7

Nadofaragene freadenovec intravesical therapy has also been evaluated in patients with BCG-unresponsive NMIBC in a phase 3 study (NCT02773849). A total of 103 patients were included in the trial, and the CR at 3 months was 53% and 24% at 12 months.8 These data suggest that nadofaragene freadenovec could be an alternative to pembrolizumab; however, it is not yet approved by the FDA or European Medicines Agency [III, C].

Due to the nature of the studies and lack of approvals for both pembrolizumab and nadofaragene freadenovec, further robust data are required before stronger recommendations can be made for their use.3

**Treatment of MIBC**

**Radical Cystectomy**

Optimal management of MIBC should include multidisciplinary care involving tumor board discussions and/or direct consultations with a medical oncologist, radiation oncologist, and urologist [IV, B]. RC with pelvic lymph node dissection remains the standard of care for MIBC CT2-T4aN0M0 [I, A].6

**Organ-preservation**

For patients unable to undergo RC or desiring an alternative, organ-preservation therapy is an option [II, B].3 Trimodal therapy incorporating a combination of TURBT, radiotherapy, and chemotherapy is recommended (II, B). Cisplatin when administered with radiotherapy improved local control rates (HR, 0.50; 90% CI, 0.29-0.86) [II,B].10

**Neoadjuvant and Adjuvant Therapy**

A meta-analysis of 11 randomized trials including 3005 patients indicates a survival benefit associated with cisplatin-based neoadjuvant chemotherapy regimens (HR, 0.86; 95% CI, 0.77-0.95). This equates to a 5% absolute increase in 5-year overall survival and a 9% absolute increase in 5-year DFS versus RC alone.11

Three to 4 cycles of cisplatin-based neoadjuvant chemotherapy is recommended; however, the optimal regimen is still unknown. A recent, randomized phase 3 trial comparing dose-dense MVAC to gemcitabine and cisplatin in patients with MIBC indicates a higher local control rate (complete pathological response, tumor downstaging, or organ-confined) with the use of MVAC (P = .021).12 However, progression-free survival (PFS) data are pending, and previous retrospective studies are mixed regarding advantages of MVAC versus cisplatin/gemcitabine.13,14

In patients unfit for cisplatin, adjuvant chemotherapy is not recommended [I, D]. An overall survival benefit (HR, 0.77; 95% CI, 0.59-0.99) and DFS benefit (HR, 0.66; 95% CI, 0.45-0.91) for patients receiving cisplatin-based adjuvant chemotherapy versus observation were shown in a meta-analysis of 9 randomized trials including 945 patients [II, B].15 However, no randomized phase 3 data are available at this time.

Adjuvant nivolumab showed promising results in the CheckMate 274 trial (NCT02632409), producing an improved DFS rate in the overall study population compared with placebo (74.9% vs 60.3%; HR, 0.70; 98.2% CI, 0.55-0.90) as well as in PD-L1-positive patients (74.5% vs 55.7%, respectively; HR, 0.53; 98.7% CI, 0.35-0.85) [I, D].16

“Nivolumab is approved in the adjuvant setting in patients who show resistance to platinum-based chemotherapy but is not yet recommended because we do not yet have survival data,” Bellmunt said. “We need to wait for survival data for adjuvant chemotherapy.”

**Management of Advanced/ Metastatic Disease**

**Cisplatin-based Chemotherapy**

The most widely used and accepted cisplatin chemotherapy regimen is gemcitabine-cisplatin for patients fit enough to tolerate it [I, A]. Alternative regimens include dose-dense MVAC [I, B]; MVAC with granulocyte colony-stimulating factor [I, B]; and gemcitabine, cisplatin, and paclitaxel (Abraxane) [I, C].

Similar results are reported with these regimens, although gemcitabine-cisplatin has a more favorable safety profile and tolerability across studies.17-19

Other regimens expanding the gemcitabine-cisplatin combination are not recommended because studies show no statistical improvement in outcomes or improvement in overall survival.20,21

Some patients are deemed unfit for cisplatin-based chemotherapy on predefined criteria established by consensus in 2011.22

For these patients, carboplatin-based chemotherapy is recommended [I, A], with the preferred combination of carboplatin and gemcitabine.23

Atezolizumab and pembrolizumab are potential alternative first-line choices for PD-L1-positive patients not eligible for cisplatin-based therapy; however, current data do not show a superior response with immune checkpoint inhibitors (ICIs) vs chemotherapy [III, B].24,25

**ESMO Levels of Evidence and Grades of Recommendation**

**Levels of Evidence**

I Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity

II Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

III Prospective cohort studies

IV Retrospective cohort studies or case-control studies

V Studies without control group, case reports, expert opinions

**Grades of Recommendation**

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional

D Moderate evidence against efficacy or for adverse outcome, generally not recommended

E Strong evidence against efficacy or for adverse outcome, never recommended

Bellmunt noted the importance of establishing PD-L1-positive status based on scoring prior to initiating therapy with pembrolizumab or atezolizumab, unless the patient is entirely chemotherapy ineligibile.

**Enfortumab Vedotin-ejfv and Pembrolizumab**

A study evaluating the combination of enfortumab vedotin-ejfv and pembrolizumab in the first-line setting for cisplatin-ineligible patients (NCT03288545) produced an objective response rate (ORR) of 73.3% (95% CI, 58.1%-85.4%). However, due to the small sample size, no recommendations for use can be made at this time.26

“The most important data within advanced and metastatic disease is from JAVELIN Bladder 100 trial [NCT02603432], where
maintenance immunotherapy with avelumab [Bavencio] has provided survival benefit for patients who are not progressing after receiving chemotherapy,” Bellmunt said.

Within 10 weeks of first-line platinum-based chemotherapy, avelumab should be initiated. Patients without disease progression after 4 to 6 cycles of gemcitabine with cisplatin or carboplatin have an overall survival (OS) advantage compared with best supportive care (HR, 0.69; 95% CI, 0.56-0.86) [I, A].27

“Unlike with other cancers, the combination of immunotherapy and chemotherapy has failed in [UC] trials compared to standard-of-care chemotherapy. So for metastatic patients, we still recommend platinum-based chemotherapy first,” Bellmunt said.

“For patients who have no progression on chemotherapy, we recommend they switch to maintenance avelumab, which has shown a substantial survival advantage.”

Relapsed Advanced/Metastatic UC

For patients with progression after platinum-based chemotherapy, pembrolizumab is recommended based on a significant survival advantage compared to chemotherapy observed in the KEYNOTE-045 trial (NCT02256436) [I, A]. Compared with chemotherapy, pembrolizumab showed a higher overall response rate (21% vs 11%) and longer median DOR (29.7 months vs 4.4 months) in the second-line setting.28,29

Chemotherapy and Immunotherapy-relapsed disease

Patients with progression after chemotherapy and maintenance avelumab should be given enfortumab vedotin-ejfv due to its superiority to chemotherapy (vinflunine or taxanes) [I, A]. Superior overall response rate (40.6% vs 17.9%), PFS (HR, 0.62; 95% CI, 0.51-0.75), and OS (HR, 0.70; 95% CI 0.56-0.89; 12.8 vs 9.0) were observed with enfortumab vedotin-ejfv versus chemotherapy.10

Bellmunt noted the lack of approval for enfortumab vedotin-ejfv in many countries in Europe but added that “there was a survival advantage for these patients [from EV-301] in the second-line setting. We are now extrapolating these data to patients who are progressing after maintenance, and enfortumab vedotin-ejfv is approved in the United States.”

There is greater evidence for enfortumab vedotin-ejfv than erdafitinib (Balversa). Erdafitinib showed an objective response rate of 40% among all patients and 59% among patients who had previously undergone immunotherapy in a phase 2 trial that evaluated 22 patients with fibroblast growth receptor (FGFR) mutations.31,32 Further, a median PFS of 5.52 months (95% CI, 4.2-6.0), and median OS of 11.3 months (95% CI, 8.0-21.1) were also observed. For the FGFR-selected population, erdafitinib is also recommended, though with less robust evidence [III, B].

Final Thoughts

To conclude, Bellmunt addressed the guidelines as a whole and noted a consideration.

“These guidelines provide evidence-based medicine recommendations, but these recommendations need to be adapted country by country, especially based on reimbursement policies.” TT

References are available on TargetedOnc.com.
TIM3 Checkpoint Is a Potential Target for Acute Myeloid Leukemia Treatment

By Lisa Astor

The immune checkpoint molecule T-cell immunoglobulin and mucin domain-3 (TIM3) has prompted growing interest and is expected to expand the armamentarium of anticancer immunotherapies.1,2 Ongoing clinical trials are exploring the potential of this checkpoint alone or as part of a dual immunotherapy regimen. Promising findings, seen both preclinically and clinically, have been reported in the setting of acute myeloid leukemia (AML), capitalizing on TIM3’s ability to kill leukemia stem cells (LSCs).

Role of TIM3

The TIM3 checkpoint is considered a promising therapeutic target because of its association with the regulation of innate and adaptive immune responses in cancer. TIM3 is a glycoprotein expressed on the surface of regulatory T cells, macrophages, natural killer cells, dendritic cells, mast cells, and myeloid cells. Investigators hypothesize that agents directed at this checkpoint could modulate immune responses on multiple cell types and thus be particularly therapeutically efficacious.2

As a receptor, TIM3 interacts with multiple ligands, including galectin-9 (Gal-9), phosphatidylserine, HMGB1, and CEACAM1. All these ligands bind to different regions of the TIM3 extracellular immunoglobulin V domain, resulting in different effects.

Gal-9 was the first ligand found to bind to TIM3. With this interaction, immune responses are suppressed as apoptosis is induced in the TIM3-expressing T cells (FIGURE).3,5 TIM3 blockade results in tumor antigen–specific T-cell proliferation, the production of proinflammatory cytokines, and functional inhibition of regulatory T cells and myeloid-derived suppressor cells.3

TIM3 overexpression may be a sign of more aggressive cancer as the protein is not often expressed in early stages of tumor development.

Singling Out AML

In AML, specifically, the interaction of gal-9 and TIM3 can activate such pathways as PI3K/mTOR to support the survival of AML cells. When the 2 receptor-binding gal-9 interact with TIM3, an autocrine loop is created that leads to LSC self-renewal and NF-κB activation, thus promoting cancer progression.1

TIM3 is highly expressed on LSCs and leukemic progenitors in most types of AML but is not expressed on normal hematopoietic stem cells.4 Investigators studying protein expression in patients with AML found that the majority of their LSCs were positive for TIM3 expression at the time of diagnosis (78.5%) and at relapse (64.7%).3 Higher TIM3 expression is also associated with worse outcomes in AML.1

Therefore, targeting TIM3-positive cells for antitumor therapy should selectively eradicate AML LSCs while sparing normal hematopoietic stem cells.4 In a preclinical study, the TIM3-targeted monoclonal antibody ATIK2, which induces complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, prevented the development of AML in xenograft models without affecting normal hematopoiesis. When mice with human AML cell xenografts were treated with ATIK2, LSCs were eliminated in vivo.4

Promising Trial Data

A number of clinical trials are exploring the potential of TIM3 inhibitors as monotherapy or combination regimens for patients with cancer. According to trial findings presented at the 2021 American Society of Hematology (ASH) Annual Meeting and Exposition, sabatolimab (MBG453) in combination with a hypomethylating agent (HMA) resulted in promising survival rates among patients with myelodysplastic syndrome (MDS) or AML.4

This multi-arm, open-label phase I study (NCT03066648) enrolled patients with high- or very high-risk MDS, relapsed or refractory AML, or de novo AML who were not candidates for standard chemotherapy and had not received prior HMA therapy. Patients in 1 cohort received the high-affinity humanized anti-TIM3 IgG4 antibody sabatolimab in combination with an HMA (decitabine or azacitidine).

The results presented at ASH 2021 were from a retrospective analysis of 28 patients who underwent allogeneic hematopoietic cell transplantation (AHCT) after the trial. The regimen consisted of 4-week cycles of escalating doses of intravenous (IV) sabatolimab every 2 or 4 weeks plus either 20 mg/m² IV decitabine (n = 12) on days 1 through 5 or 75 mg/m² IV azacitidine (n = 16) on days 1 through 7.

The median age was 67 years (range, 23-77) and 64% were male. Sixty-eight percent of patients had MDS, 21% had AML, and 11% had chronic myelomonocytic leukemia. The cytogenetic risk status was adverse in...
48% of patients, 33% had a complex karyotype, and 50% had a high-risk mutation.

Prior to AHCT, 36% of patients had a complete response (CR), 32% had a molecular CR or CR with incomplete hematologic recovery, 8% had a partial response or hematologic improvement, and 25% had stable disease.

Andrew M. Brunner, MD, an assistant professor of medicine at Harvard Medical School and assistant in medicine at the Center for Leukemia at Massachusetts General Hospital, noted that transplant outcomes in this group were generally favorable.

Following AHCT, median overall survival (OS) was not reached, but the 2-year OS rate was 69% and the 2-year recurrence-free survival rate was 64%.

No associations were found between OS and disease type ($P = .84$), but patients with $TP53$ wild-type disease ($n = 21$) had significantly improved OS ($P < .01$). Surprisingly, patients with $RAS$ mutations ($n = 6$), which have been associated with worse outcomes in other studies, did have significantly different responses compared with those with $RAS$ wild-type disease ($P = .66$).

Brunner said that in this cohort, toxicities related to graft-vs-host disease (GVHD) were in line with historical rates. Fifty-seven percent of patients experienced acute GVHD, and grade 3/4 acute GVHD was reported in 14%. One patient with grade 4 acute GVHD died on hospice. Chronic GVHD leading to the need for systemic immunosuppression was reported in 29% of patients.

The combination of sabatolimab and azacitidine is being further explored in a phase 1/2 trial in patients with primary or secondary AML in CR following AHCT but who have measurable residual disease (NCT04623216). Additionally, the phase 2 STIMULUS-AML trial (NCT04623216) is investigating the use of sabatolimab and azacitidine plus venetoclax (Venclexta) in patients with newly diagnosed AML unfit for intensive chemotherapy.

**Future TIM3 Approaches in AML**

In addition to monoclonal antibodies such as sabatolimab, regimens that investigators are exploring include TIM3 chimeric antigen receptor therapy and combinations of TIM3 inhibitors with cancer vaccines, PD-1 inhibitors, or chemotherapy in an effort to enhance the efficacy of these therapeutics for patients with AML.

As interest in TIM3 blockade in AML continues to grow, research efforts hope to elucidate the function of this checkpoint molecule in AML and reveal additional ways of targeting it to fight cancer.

**Broadening MTB’s Role Could Improve Response and Survival Rates in Women’s Cancers**

By Tony Berberabe, MPH

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**EXPANDING THE USE** of multidisciplinary tumor boards (MTBs) to help guide treatment decisions and match therapies has demonstrated positive outcomes in patients with gynecologic and breast cancers, according to findings from investigators at the Moores Cancer Center at UC San Diego Health. When investigators matched therapies with patients whose genomic alterations were identified through next-generation sequencing (NGS), it revealed higher overall response rates and progression-free survival (PFS), and a trend toward improved overall survival (OS).

Using NGS to help inform treatment options is growing in frequency, but the results can be difficult to interpret and implement in clinical practice. Multiple institutions have implemented MTBs to help clinicians improve outcomes in patients.

A total of 164 female patients with breast (n = 128; 78.0%) and ovarian (n = 36; 22.0%) cancers were presented to the UC San Diego MTB. Overall, 113 patients were evaluable for treatment after review by the MTB. Sixty-one patients (54%) received matched therapy. Investigators calculated the matching score, which was the percentage of alterations targeted by treatment over total pathogenic alterations, and adherence to MTB recommendations in the context of oncologic outcomes. For evaluable patients, the median PFS was 5.1 months (range, 0.4-73.5) and OS was 12.9 months (range, 0.7-73.5). Patients with an MS of less than 40% (n = 87) had a median PFS of 3.9 months (range, 0.4-73.5), whereas patients with an MS of 40% or greater (n = 26) had a median PFS of 9.3 months (range, 1.4-19.0; HR, 0.51; 95% CI, 0.31-0.85; $P = .002$; **TABLE**).

In univariate analysis, patients with an MS greater than 40% had a higher overall response rate vs those whose MS was less than 40% (30.8% vs 7.1%; $P = .001$). They also had a higher PFS (HR, 0.31; 95% CI, 0.31-0.85; $P = .002$) and a trend toward improved survival.
INVESTIGATOR PERSPECTIVES with the latest clinical trial updates

The Investigator Perspectives video series features an expert discussing the latest clinical trial updates and patient care management.

Are Combinations the Answer in Metastatic RCC?

Robert J. Motzer, MD, provides perspective on recent data from the phase 3 CLEAR trial (Study 307)/KEYNOTE-581 for advanced renal cell carcinoma.

The investigators recommended expanding the role of MTBs to assist with treatment decisions for patients with breast and gynecologic cancers as it could lead to improved response rates and outcomes.

**TABLE.** PFS AND OS OF PATIENTS WHO PRESENTED AT MTB (N = 113)

<table>
<thead>
<tr>
<th>MS</th>
<th>MEDIAN PFS (MONTHS; RANGE)</th>
<th>P VALUE</th>
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<tbody>
<tr>
<td>All patients (n = 113)</td>
<td>5.1 (0.4-73.5)</td>
<td></td>
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<tr>
<td>&lt; 40% (n = 87)</td>
<td>3.9 (0.4-73.5)</td>
<td>.002</td>
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<tr>
<td>≥ 40% (n = 26)</td>
<td>9.3 (1.4-19.0)</td>
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<table>
<thead>
<tr>
<th>MS</th>
<th>MEDIAN OS (MONTHS; RANGE)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 113)</td>
<td>12.9 (0.7-73.5)</td>
<td></td>
</tr>
<tr>
<td>&lt; 40% (n = 87)</td>
<td>11.9 (0.7-73.5)</td>
<td>.082</td>
</tr>
<tr>
<td>≥ 40% (n = 26)</td>
<td>18.8 (1.5-44.4)</td>
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</tbody>
</table>

MS, matched score; MTB, multidisciplinary tumor board; OR, overall survival; PFS, progression-free survival.
Indication
VITRAKVI (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. Select patients for therapy based on an FDA-approved test. 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 confirmatory trials.

Important Safety Information
Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances. In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients. Cognitive impairment occurred in 11% of patients. The median time to onset of cognitive impairment was 5.6 months (range: 2 days to 41 months). Cognitive impairment occurring in ≥1% of patients included memory impairment (3.6%), confusional state (2.9%), disturbance in attention (2.9%), delirium (2.2%), cognitive disorders (1.4%), and Grade 3 cognitive adverse reactions occurred in 2.5% of patients. Among the 30 patients with cognitive impairment, 7% required a dose modification and 20% required dose interruption.

Please see additional Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information.
NTRK, neurotrophic receptor tyrosine kinase; TRK, tropomyosin receptor kinase.

Fractures of the femur, hip or acetabulum were reported in (range 0.9 to 45.8 months) in patients followed per fracture.

VITRAKVI across clinical trials, fractures were reported in 7% of patients. Among the 187 adult patients who received VITRAKVI, increased AST (52%), increased ALT (45%), anemia (42%), nausea (39%), constipation (39%), vomiting (25%), pyrexia (24%), lymphopenia (22%) and diarrhea (20%) were the most common ALT of any grade occurred in 45%. Grade 3-4 increased AST occurred in 52% of patients and increased ALT occurred in 45%. Grade 3 mood disorders occurred in 14% of patients. The median time to onset of mood disorders was 3.9 months (range: 1 day to 40.5 months). Mood disorders occurring in ≥1% of patients included anxiety (5%), depression (3.9%), agitation (2.9%), and irritability (2.9%). Grade 3 mood disorders occurred in 0.4% of patients. Dizziness occurred in 27% of patients, and Grade 3 dizziness occurred in 1.1% of patients. Among the 74 patients who experienced dizziness, 5% of patients required a dose modification and 5% required dose interruption. Sleep disturbances occurred in 10% of patients. Sleep disturbances included insomnia (7%), somnolence (2.5%), and sleep disorder (0.4%). There were no Grade 3-4 sleep disturbances. Among the 28 patients who experienced sleep disturbances, 1 patient each (3.6%) required a dose modification or dose interruption. Advise patients and caretakers of these risks with VITRAKVI.

Skeletal Fractures: Among 187 adult patients who received VITRAKVI across clinical trials, fractures were reported in 7% and among 92 pediatric patients, fractures were reported in 9% (N=279, 8%). Median time to fracture was 11.6 months (range 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). Most fractures were associated with minimal or moderate trauma. Some fractures were associated with radiologic abnormalities suggestive of local tumor involvement. VITRAKVI treatment was interrupted due to fracture in 1.4% patients. Promptly evaluate patients with signs or symptoms of potential fracture (e.g., pain, changes in mobility, deformity). There are no data on the effects of VITRAKVI on healing of known fractures or risk of future fractures.

Hepatotoxicity: In patients who received VITRAKVI, increased AST of any grade occurred in 52% of patients and increased ALT of any grade occurred in 45%. Grade 3-4 increased AST or ALT occurred in 3.1% and 2.5% of patients, respectively. The median time to onset of increased AST was 2.1 months (range: 1 day to 4.3 years). The median time to onset of increased ALT was 2.3 months (range: 1 day to 4.2 years). Increased AST and ALT leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 3 (1.1%) of patients. Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

Embryo-Fetal Toxicity: VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily.

*Fusion positive indicates a disease stage in which the presence of an NTRK gene fusion is critical for the growth of tumor cells and negative margins were pathological complete responders.

**Based on medical claims and prescription data claims for the period August 2019 through December 2020. Validated by IQVIA in March 2021.
IN NTRK GENE FUSION–POSITIVE SOLID TUMORS, INHIBIT WHAT’S DRIVING THE TUMOR WITH VITRAKVI FOR:

Robust responses

- In the primary data set (N=55)
  - 25% CR\(^\text{a,b}\) (n=14/55)
  - 49% PR\(^\text{a}\) (n=27/55)

75% ORR\(^\text{a}\) (95% CI: 61%, 85%) (n=41/55)

1 in 4 patients had a complete response\(^{\text{a,b}}\)

Demonstrated durability

32.9-month mDOR\(^{\text{c}}\)

(95% CI: 14.8, NE\(^{*}\))

(Range: 1.6+ to 50.6+ months)

\(^{\text{a}}\) CR, complete response; ORR, overall response rate; PR, partial response.

\(^{\text{b}}\) 5% were pathological complete response. Patients undergoing a surgical resection whose postoperative pathologic assessment showed no viable tumor were counted as pathological complete responders.

\(^{\text{c}}\) mDOR, median duration of response; NE, not evaluable.

Find the oncogenic driver early and act with VITRAKVI for appropriate patients

TEST. TRK. TREAT.

Study design: A pooled efficacy analysis based on 3 open-label, single-arm clinical studies in adult and pediatric patients with unresectable or metastatic solid tumors with an NTRK gene fusion. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Major efficacy outcome measures were ORR and DOR\(^{\text{d}}\), as determined by a BIRC\(^{\text{e}}\) according to RECIST\(^{\text{v1.1}}\).

\(^{\text{d}}\) ORR, overall response rate; DOR, duration of response; RECIST, Response Evaluation Criteria in Solid Tumors.

\(^{\text{e}}\) BIRC, blinded independent review committee; DOR, duration of response; RECIST, Response Evaluation Criteria in Solid Tumors.

Indication

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. Select patients for therapy based on an FDA-approved test. 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 confirmatory trials.

Important Safety Information (continued)

Embryo-Fetal Toxicity (continued): Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

Most Common Adverse Reactions (≥20%): The most common adverse reactions (≥20%), including laboratory abnormalities, were: increased AST (52%), increased ALT (45%), anemia (42%), musculoskeletal pain (42%), fatigue (36%), hypoalbuminemia (36%), neutropenia (36%), increased alkaline phosphatase (34%), cough (32%), leukopenia (28%), constipation (27%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (25%), vomiting (25%), pyrexia (24%), lymphopenia (22%) and abdominal pain (21%).

Drug Interactions: Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John’s wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Lactation: Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

Please see Brief Summary of full Prescribing Information on the following page.
All patients had an unresectable or metastatic solid tumor and no satisfactory alternative treatment for greater than 1 year. VITRAKVI was studied in one adult dose-finding trial (LOXO-TRK-14001 (n = 75)).

- Hepatotoxicity [see Warnings and Precautions (5.1)]

- Central Nervous System Effects

The following clinically significant adverse reactions are described elsewhere in the labeling: [see Use in Specific Populations (8.1, 8.3)]

- Increased ALT and AST (4.3%), and neutrophil count decreased (4.3%). Most (70%) adverse reactions leading to dose interruption or modification occurred in 39% and 8% of patients, respectively, and 9% permanently discontinued VITRAKVI for adverse reactions. The most common adverse reactions (1%, each) that resulted in permanent discontinuation of VITRAKVI were increased ALT, dizziness, and fatigue. The most common adverse reactions (> 3%) resulting in dose interruption were increased ALT (4.7%), increased AST (4.3%), and neutropil count decreased (4.3%). Most (70%) adverse reactions leading to dose interruption occurred during the first three months of exposure. Adverse reactions of VITRAKVI occurring in ≥ 10% of patients and laboratory abnormalities worsening in 10% of patients are summarized in Table 2 and Table 3, respectively.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3-4***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucositis and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>42</td>
<td>3.9</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>2.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Neuropsychiatric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>27</td>
<td>1.1</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>1.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>0.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>0.6</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood disorders</td>
<td>14</td>
<td>0.4</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>1.4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>1.4</td>
</tr>
</tbody>
</table>

The adverse reaction identifies a composite term: Includes: arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

Includes: fatigue, anemia.

Includes: face edema, generalized edema, lip edema, localized edema, edema, edema genital, edema peripheral, periorbital edema, and swelling.

Includes: cough, productive cough, and upper-airway cough syndrome

Includes: dysraphism, and hypoplastic excretion.

Includes: dizziness, dizziness postural, and vertigo

Includes: amnesia, aphasia, cognitive disorder, confusion, delirium, disturbance in attention, hallucination, memory impairment, mental impairment, mental status changes

Includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain

Includes: dermatitis, dermatitis acrodermatitis, dermatitis bullous, dermatitis exfoliative generalisata, eczema, eczema ascolatilis, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash macular-papular, rash papular, rash pruritic, and rash purpura

Includes: agitation, anxiety, depression, depressed mood, euphoria, mood lability

Includes: insomnia, sleep disorder, somnolence

Includes: cystitis, escherichia urinary tract infection, pyelonephritis acute, and urinary tract infection

*National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.

**Grade 4 adverse reaction of pyelonephritis.

Clinically relevant adverse reactions occurring in ≥ 10% of patients include fractures (8%).
The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in adult or pediatric patients 28 days and older [see Adverse Reactions (6.1), Clinical Studies (14)]. The efficacy of VITRAKVI was evaluated in 17 pediatric patients and is described in the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was evaluated in 50 pediatric patients (median age 10.6 years). At least one patient received VITRAKVI. Of these 92 patients, 88 were <1 month to <2 years (n = 33), 41 were 2 years to <12 years (n = 38), and 23 were 12 years to <18 years (n = 21); 29% had metastatic disease, 42% had locally advanced disease, and 27% had primary CNS disease. 88% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were infantile fibrosarcoma (37%), primary CNS tumors (27%), soft tissue sarcoma (24%), and thyroid cancer (7%). The median duration of exposure was 0.7 months (range: 0.1 months to 37 months).

Table 3 Laboratory Abnormalities Occurring in ≥ 20% Patients Treated with VITRAKVI

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>52</td>
<td>3.3</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>46</td>
<td>2.5</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>12.3</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>Hematuria</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td>26</td>
<td>1.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>12</td>
<td>1.4</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>22</td>
<td>6</td>
</tr>
</tbody>
</table>

- **Increased AST**
- **Hypoalbuminemia**
- **Increased alkaline phosphatase**
- **Hyperbilirubinemia**
- **Hematuria**
- **Anemia**
- **Neutropenia**
- **Lymphopenia**

**Chemistry**

Increased AST 52 3.3
Hypoalbuminemia 46 2.5
Increased alkaline phosphatase 36 12.3
Hyperbilirubinemia 25 2.6
Hematuria 42 10
Anemia 36 1.4
Neutropenia 12 1.4
Lymphopenia 22 6

*Based on NCI CTCAE v4.03
**Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 272 to 277 patients.

7. DRUG INTERACTIONS

7.1 Effects of Other Drugs on VITRAKVI

Co-administration of VITRAKVI with a strong CYP3A4 inhibitor may increase larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If co-administration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

Strong CYP3A4 Inducers

Avoid co-administration of VITRAKVI with strong CYP3A4 inducers, including St John’s wort, if co-administration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

7.2 Effects of VITRAKVI on Other Drugs

Avoid co-administration of VITRAKVI with strong CYP3A4 inducers may decrease larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inducers, including St John’s wort, if co-administration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.3)], VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman. There is no available data on VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily (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

Human Data

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and adipogenesis.

Animal Data

Larotrectinib crosses the placenta in animals. Larotrectinib did not result in embryoembryopathy at maternally toxic doses (up to 40 times the human exposure based on area under the curve (AUC) at the clinical dose of 100 mg twice daily) in early embryo-fetal development studies in pregnant rats dosed during the period of organogenesis; however, larotrectinib was associated with fetal anasarca in rats from dams treated at twice-daily doses of 40 mg/kg (11 times the human exposure (AUC) at the clinical dose of 100 mg twice daily). In pregnant rabbits, larotrectinib administration was associated with embryonic death at twice-daily doses of 15 mg/kg (0.7 times the human exposure at the clinical dose of 100 mg twice daily).

8.2 Lactation

Risk Summary

There are no data on the presence of larotrectinib or its metabolites in human milk and no data on its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with larotrectinib and for 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating VITRAKVI [see Use in Specific Populations (8.4)].

Contraception

VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.4)].

Females

Advise female patients of reproductive potential to use effective contraception during treatment with VITRAKVI and for at least 1 week after the final dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with VITRAKVI and for 1 week after the final dose.

Infertile Females

Based on histopathological findings in the reproductive tract of female rats in a 1-month repeated-dose study, VITRAKVI may reduce fertility [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of VITRAKVI in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in adult or pediatric patients 28 days and older [see Adverse Reactions (6.1), Clinical Studies (14)].

The efficacy of VITRAKVI was evaluated in 17 pediatric patients and is described in the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was evaluated in 50 pediatric patients. Central Neurovascular (1%) and peripheral, periorbital edema, and swelling (1%) were reported in ≥ 1% of patients. Intracranial hemorrhage occurred in 3 patients (2%), and cerebral edema occurred in 2 (1%).

9 WARNINGS AND PRECAUTIONS

9.1 General Information

Sensitivity CYP3A4 Substrates

Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If co-administration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

Strong CYP3A4 Inducers

Avoid co-administration of VITRAKVI with strong CYP3A4 inducers may decrease larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI [see Clinical Pharmacology (12.3)]. Avoid co-administration of VITRAKVI with strong CYP3A4 inducers, including St John’s wort, if co-administration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

9.4 Tubuloglomerular Feedback

Avoid co-administration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If co-administration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].
New Clinical Trials by State

Targeted Oncology™ offers an online resource that filters by state and disease type to help oncologists find studies in their practice area.

Scan the QR code to find more trials in your practice area or visit targetedonc.com/link/1312

Ohio

**DISEASE TYPE** Triple-Negative Breast Cancer

**CLINICAL TRIAL** NCT04674306

An open-label, dose-escalation phase 1 trial is looking at treatment with the α-lactalbumin vaccine and zymosan in patients with high-risk triple-negative breast cancer. The vaccine is expected to stimulate the immune system to fight off the participant's cancer. The estimated study completion date is September 2022.

Approximately 24 patients will be enrolled and treated with successively higher doses of the regimen. At dose level 1, both the vaccine and the adjuvant zymosan would be administered at 10 mcg; 100 mcg at dose level 2; and 1000 mcg at dose level 3. Three vaccinations will be administered subcutaneously every 2 weeks.

Eligible patients are those with invasive breast cancer either of stage IIA to IIIC or with residual disease in the breast or regional lymph nodes following preoperative chemotherapy. Additionally, patients must have an ECOG performance status of 0 or 1 and adequate major organ function. Recruitment has begun at the Cleveland Clinic with investigator George T. Budd, MD.

For more details, visit targetedonc.com/link/1547

Texas

**DISEASE TYPE** Advanced Solid Tumors

**CLINICAL TRIAL** NCT05012397

A multicenter, single-arm, open-label phase 2 basket study is looking at milademetan (RAIN-32) in patients with advanced or metastatic solid tumors refractory or intolerant to standard-of-care therapy with wild-type TP53 and MDM2 amplification. The estimated study completion date is August 2024.

Approximately 65 patients will be enrolled and treated with the oral MDM2 inhibitor at 260 mg once daily on days 1 to 3 and days 15 to 17 of each 28-day cycle.

Eligible patients have locally advanced or metastatic solid tumors and measurable disease. Patients should have received all standard, appropriate therapies or must be unlikely to benefit from such therapies. Additionally, patients should have an ECOG performance status of 0 or 1 and adequate bone marrow, renal, and hepatic function.

Recruitment has begun at The University of Texas MD Anderson Cancer Center in Houston.

For more details, visit targetedonc.com/link/1546
APOLLO 613 is an open-label phase 1/2 trial looking at the use of devimistat (CPI-613) and hydroxychloroquine in patients with relapsed or refractory clear cell sarcomas of the soft tissue. Devimistat is designed to target the mitochondrial tricarboxylic acid cycle, an essential part of tumor cell proliferation and survival, and is intended to increase cellular stress while increasing the sensitivity of cancer cells to a diverse range of chemotherapeutic agents. The estimated study completion date is November 2024. Approximately 47 patients are expected to be enrolled and treated with 2.5 mg/kg oral hydroxychloroquine followed by 1000 mg/m² of intravenous devimistat 2 hours later, given over a course of 2 hours. This is to be followed by 2.5 mg/kg oral hydroxychloroquine 12 hours after the initial dose daily for the first 5 days of every 28-day cycle. Eligible patients are between 11 and 75 years old. Those under 18 years should have a Karnofsky performance status above 60, and patients 18 years or older should have an ECOG performance status of 0 to 2. Patients with Ewing sarcoma are only eligible for phase 1 of the study. All patients should have received at least 1 prior line of therapy and those with TRK fusion-positive tumors must have received a prior TRK inhibitor. Patients must also have adequate bone marrow, renal, liver, and neurologic function as well as blood pressure control. Those with bone marrow metastatic disease are eligible if they meet specified blood counts, but will not be eligible for hematologic toxicity.

Recruitment has begun at City of Hope in Duarte with Mark Agulnik, MD. For more details, visit targetedonc.com/link/1545

IMforte is a randomized, open-label, multicenter phase 3 trial of lurbinectedin (Zepzelca) in combination with atezolizumab (Tecentriq) vs atezolizumab alone as maintenance therapy for patients with extensive-stage small cell lung cancer (ES-SCLC) after first-line therapy with carboplatin, etoposide, and atezolizumab. Lurbinectedin has already made a difference in clinical outcomes for patients with SCLC in the second-line setting. The IMforte trial aims to add the agent to a first-line immunotherapy regimen for ES-SCLC. The study will consist of both an induction and a maintenance phase. The estimated study completion date is March 2025. Approximately 690 patients will be enrolled and randomized in a 1:1 fashion. In the induction phase, all patients will receive the PD-L1 inhibitor at 1200 mg intravenously on day 1 of each 21-day cycle plus carboplatin on day 1 and etoposide on days 1 to 3 of each cycle for 4 cycles. In the maintenance phase, patients are to receive intravenous atezolizumab at 1200 mg with or without intravenous lurbinectedin at 3.2 mg/m², both administered on day 1 of each cycle. Eligible patients for the induction phase have ES-SCLC with no prior systemic treatment for extensive-stage disease and an ECOG performance status of 0 or 1. They must have adequate hematologic and end-organ function as well as no HIV or active hepatitis B or C. Patients must be treatment free from chemotherapy/radiotherapy for at least 6 months for limited-stage SCLC. For the maintenance phase, patients must have had ongoing response or stable disease by RECIST criteria after 4 cycles of therapy and all toxicities related to induction therapy had to be resolved to grade 1 or lower. Patients with central nervous system metastasis, autoimmun disease or deficiency, or other prior malignancy are not eligible for enrollment. Recruitment has begun at Northwest Georgia Oncology Centers in Marietta and at Illinois CancerCare in Peoria. For more details, visit targetedonc.com/link/1543
HOME TO APPROXIMATELY 4.5 million Americans, Kentucky sees more individuals die of cancer than any other state. Cancer mortality in Kentucky is 17% higher than the overall cancer mortality rate in the United States, according to the most recent information available from the CDC. Kentucky also has the nation’s highest rate of lung cancer.

Years of research by scientists, oncologists, and other clinicians in the community setting have revealed the big picture of lung cancer occurrence and outcomes in Kentucky. Some have begun to investigate potential causes such as regional disparities, smoking rates, and discrepancies in legislation. Research has highlighted that patients in the Appalachian communities of Kentucky are heavily impacted by lung cancer.

“I take care of a lot of lung cancer patients, and it is definitely a challenge but rewarding to be a part of their care,” said Adam D. Lye, MD, medical oncologist/hematologist, Norton Cancer Institute, Louisville, Kentucky, in an interview with Targeted Therapies in Oncology. “We typically see patients at a more advanced stage of lung cancer. This may be due, in some areas, to lack of education about the disease and lack of access to oncology care.

“Also, this issue has unquestionably been compounded during the [COVID-19] pandemic with so many patients waiting to return for medical care and also avoiding going to the doctor despite the presence of lung cancer symptoms,” he added. “Our organization has focused on the importance of lung cancer screening to detect these cancers as early as possible when treatment is more likely to result in curative intent. Education and awareness of lung cancer screening continue to be a challenge throughout our state and others.”

Kentucky vs the United States

According to a recent study by investigators at the University of Kentucky’s Research Department and physicians in the Markey Cancer Center in Lexington, considerable disparities exist between the population of patients with lung cancer in Kentucky and the rest of the United States. The disparities reportedly contribute to a higher cancer burden as well as poorer survival outcomes.

“We do have the highest rate of lung cancer and because of that we also have a higher mortality. It’s interesting to note that there are many different types of lung cancer. In Appalachian Kentucky and Kentucky as a whole, we see a shift in subtype distribution, so we have more squamous cell carcinomas (SCC) and more small cell lung cancer (SCLC), which are particularly aggressive and deadly. That’s an obvious concern for us here because not only do we have more lung cancer overall per person, but we also have an increase in these types of cancers that are harder to treat,” Christine F. Brainson, PhD, assistant professor of toxicology and cancer biology at the University of Kentucky College of Medicine, told Targeted Therapies in Oncology in an interview.

The University of Kentucky study aimed to better understand the key differences in lung cancer between Kentucky and the greater United States. The Surveillance, Epidemiology, and End Results (SEER) database was utilized to conduct the analysis. Investigators found 18 SEER registries for cases of patients with primary invasive malignant lung and bronchus disease who received diagnoses between 2012 and 2016. Patients evaluated were 20 years or older and had common lung cancer subtypes like adenocarcinoma, SCLC, SCC, and neuroendocrine histology, along with others (TABLE). Cases of patients with noninvasive lung cancers were excluded from the analysis.
“Overall, we had hundreds of cases in the SEER registry. We looked at the different types of lung cancers, by the pathologist code, and we also looked at incidence data and survival. All of those metrics were very different in Kentucky and especially Appalachian Kentucky. Whatever we saw in Kentucky was skewed from the national averages,” Brainson said.

The study showed a significant difference in histological distributions and incidences of lung cancer in Kentucky compared with other states in the SEER database. Incidences of adenocarcinoma were lower in non-Appalachian Kentucky compared with other state registries (25% vs 45%; P<.0001), whereas cases of SCC (25% vs 19%; P<.0001) and SCLC (17% vs 12%; P<.0001) were notably higher. All other histologies appeared to occur at similar rates as shown in the other states’ SEER registries.

“In almost every way, there are increases in absolute numbers and proportions,” Ralph Zinner, MD, professor, Division of Medical Oncology, University of Kentucky College of Medicine, said in an interview with Targeted Therapies in Oncology™. Brainson added, “But then in Appalachian Kentucky, it was even more dramatic of a change.”

Hot Spot in the Appalachian Mountains

In comparison with non-Appalachian Kentucky at 34%, patients with lung cancer in the Appalachian Mountains of Kentucky had a lower proportion of lung adenocarcinoma (29%) but a higher number of SCC cases (25% vs 27%, respectively).3

Data also showed that women in Appalachian Kentucky were more likely to be diagnosed with SCLC than others in the United States, including those in non-Appalachian Kentucky. Moreover, men in Appalachian Kentucky had a significantly higher proportion of SCCs compared with the rest of the nation.

What stood out the most about Appalachian Kentucky was the prevalence of SCLC, according to Brainson. The rates provide a signal about what a key contributor toward the high lung cancer rates in the Appalachian region may be.

“There were very evident differences in total rates of small cell [lung cancer] in the Kentucky population compared with the SEER database overall. which is important for all kinds of reasons. It corroborates the understanding of the relationship between smoking and cancer with small cell [lung cancer] being especially attached to smoking,” said Zinner.

Lye agreed, adding, “I think that patient education on the importance of smoking cessation, lung cancer screening, and seeking medical care are a continued challenge and opportunity for growth. Access to oncology medical care has been a challenge in many of these rural areas. There are also data that show even when correcting for smoking prevalence in some of these areas, the increased incidence of lung cancer may be influenced by other environmental factors. I think more research should be conducted in how the environment itself in these geographical areas may multiply the detrimental effects of cigarette use.” However, in Kentucky, some communities may be hindered in pushing forth smoking cessation education given the lack of a state law.

Unbridled Smoking and Other Contributing Factors

The road to regions having smoke-free areas in Kentucky has been long. It began in 2015 with U.S. HB145, a comprehensive smoke-free bill that was presented to the Kentucky General Assembly. The bill passed the House after amendments were made, but never reached the state Senate.5

Kentucky’s problem was a key part of the American Lung Association’s (ALA) State of Tobacco Control 2021. The organization recommended that the state government repeal the rights of local governments to control tobacco ordinances, restore funding of $3.3 million to the Kentucky Tobacco Prevention and Cessation Program, and support and defend smoke-free laws across the state. The CDC recommended that Kentucky commit $56 million to tobacco use prevention and cessation. At the time ALA published its recommendations, smoking cost Kentucky’s economy an estimated $19.1 million, with 23.6% of adults and 8.9% of high school students being smokers, and nearly 9000 deaths per year attributed to the habit.5

The problem was and is that tobacco production accounts for 50% of Kentucky’s agricultural economy, and tobacco product sales make up a significant percentage of the overall economy. Legislation known as Tobacco 21, intended to target smoking and tobacco product use among children and teens, was signed into law in August 2020.6

In response, Big Tobacco began lobbying and advertising efforts that largely left out adults and those affected by secondhand smoke.

Roughly 36.6% of residents in Kentucky are now protected by smoke-free ordinances.7 “In my area of greater metropolitan Louisville, I am not aware of any areas that allow cigarette use inside a facility. However, I know that in other areas of the state, smoking is still allowed inside some facilities. Unquestionably, the higher percentage of smokers in these areas is likely leading to pressure to resist smoke-free ordinances and policies. I think this can be improved with education and awareness in the local communities for the benefit of the entire population,” Lye explained.

Among the 63.4% of Kentucky residents not protected by smoke-free ordinances, many are in Appalachia. In some cases, entire counties have opted out of implementing smoke-free ordinances against the recommendation of health regulators in the country. These include Daviess, Franklin, Hopkins, Kenton, and Letcher counties. In these counties, lung cancer is the leading cause of cancer death, according to the most up-to-date data from the Kentucky Cancer Registry.

Smoking is just one of the potential causes of Kentucky’s high rate of lung cancer and lung cancer mortality. When asked about contributing factors, Lye stated: “The first factor is the high smoking rate. I have seen estimates that as many as 1 in 4 Kentuckians smoke tobacco. A second factor is obesity and less than optimal lifestyles. Our state is currently in the top 5 states for obesity and the No. 1 state for childhood obesity. Poor overall health is undoubtedly an additional risk factor for many cancers. Finally...there is likely an environmental factor in play as well,” Lye concluded.

### Table. Common Lung Cancer Subtypes in Kentucky

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>ALL SEER CASES</th>
<th>NON-APPALACHIAN CASES</th>
<th>APPALACHIAN CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>111,886</td>
<td>4234</td>
<td>1865</td>
</tr>
<tr>
<td>Squamous</td>
<td>48,239</td>
<td>3054</td>
<td>1740</td>
</tr>
<tr>
<td>Other</td>
<td>51,502</td>
<td>2592</td>
<td>1459</td>
</tr>
<tr>
<td>Small cell</td>
<td>29,176</td>
<td>2084</td>
<td>1178</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>9452</td>
<td>440</td>
<td>194</td>
</tr>
</tbody>
</table>

SEER, Surveillance, Epidemiology, and End Results.
Serious bacterial, mycobacterial, fungal and viral infections have occurred.

Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and...

Overall response rate was defined as the proportion of patients with complete response or partial response, according to 2014 NIH consensus criteria, at Week 24.1

In the Jakafi Prescribing Information, efficacy was based on ORR through Week 24 (Cycle 7 Day 1).2

Defined as proportion of patients who achieved complete or partial response, according to 2014 NIH Response Criteria, through Week 24 (Cycle 7 Day 1).2

Another systemic therapy for cGVHD.1

Clinical guidelines recommend delaying starting Jakafi until active serious infections have resolved. Observe patients for signs of infection and manage promptly.

Evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi if any of these occur after discontinuation or while tapering Jakafi.

Myeloproliferative neoplasm-related symptoms may occur rather than abrupt discontinuation for reasons other than thrombocytopenia or neutropenia, consider gradual tapering.
**Intervene With Jakafi® (ruxolitinib) at the First Sign of Initial Systemic Treatment Failure Regardless of Organs Involved**

Overall Response Rates Were Higher With Jakafi at Week 24 Regardless of Organs Involved at Baseline vs BAT³

**REACH3 Subgroup Analysis:**

<table>
<thead>
<tr>
<th>ORR at Week 24 by Baseline Organ Involvement³, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients %</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>52.9% (84/121)</td>
</tr>
<tr>
<td>25.7% (29/111)</td>
</tr>
<tr>
<td>0.051 (95% CI: 0.026, 0.100)</td>
</tr>
<tr>
<td>Mouth</td>
</tr>
<tr>
<td>51.5% (56/97)</td>
</tr>
<tr>
<td>29.1% (39/133)</td>
</tr>
<tr>
<td>0.036 (95% CI: 0.018, 0.067)</td>
</tr>
<tr>
<td>Eyes</td>
</tr>
<tr>
<td>45.4% (44/97)</td>
</tr>
<tr>
<td>26.1% (24/92)</td>
</tr>
<tr>
<td>0.002 (95% CI: 0.001, 0.004)</td>
</tr>
<tr>
<td>Lungs</td>
</tr>
<tr>
<td>40.5% (40/99)</td>
</tr>
<tr>
<td>25.4% (21/83)</td>
</tr>
<tr>
<td>0.007 (95% CI: 0.004, 0.012)</td>
</tr>
<tr>
<td>Joints and Fascia</td>
</tr>
<tr>
<td>43.8% (21/48)</td>
</tr>
<tr>
<td>16.7% (7/42)</td>
</tr>
<tr>
<td>0.001 (95% CI: 0.001, 0.004)</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>47.6% (20/42)</td>
</tr>
<tr>
<td>27.5% (11/40)</td>
</tr>
<tr>
<td>0.004 (95% CI: 0.002, 0.008)</td>
</tr>
<tr>
<td>GI Tract</td>
</tr>
<tr>
<td>51.3% (20/39)</td>
</tr>
<tr>
<td>25.0% (17/68)</td>
</tr>
<tr>
<td>0.005 (95% CI: 0.003, 0.010)</td>
</tr>
<tr>
<td>Genital Tract</td>
</tr>
<tr>
<td>42.9% (4/14)</td>
</tr>
<tr>
<td>17.6% (1/17)</td>
</tr>
<tr>
<td>0.178 (95% CI: 0.079, 0.390)</td>
</tr>
</tbody>
</table>

Patients with >1 affected organ were counted in each organ subgroup. ORR at Baseline was calculated as organ score ≥1 based on the cGVHD staging criteria.³

³ Patients included in the study were 12 years and older, had undergone allogeneic HSCT from any donor source/type, and had evident myeloid and platelet engraftment.³

³ BAT was chosen by the investigator prior to randomization, options included: ibritumomab, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, matinib, infliximab, or pentostatin.¹,³

³ Steroid-refractory disease was defined as lack of response or disease progression after ≥1 week of prednisone 1 mg/kg/day, disease persistence without improvement after ≥4 weeks of prednisone >0.5 mg/kg/day or 1 mg/kg every other day, or increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose.³

**REACH3**

a randomized, open-label, multicenter, Phase 3 study of Jakafi vs BAT in patients with steroid-refractory cGVHD (N = 329).¹,²,³ The starting dose for Jakafi was 10 mg BID. Crossover from BAT to Jakafi was permitted on or after Week 24 if patients progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare.¹

³ Other JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NHL (compared to those treated with TNF-blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NHL), patients who develop a malignancy, and patients who are current or past smokers.

In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥5%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections.

Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.

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

**Visit hcp.Jakafi.com to learn more**

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

**References:**
Myelofibrosis

The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg or twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 x 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 x 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia (see Table 2).

Thrombocytopenia, anemia, and neutropenia are dose-related effects. The three most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment were bruising, dizziness, and headache (see Table 1). Discontinuation of treatment may result of dizziness was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-Blind, Placebo-Controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Jakafi (N=157)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td>All Grades</td>
</tr>
<tr>
<td>Bruising*</td>
<td>23</td>
</tr>
<tr>
<td>Dizziness*</td>
<td>18</td>
</tr>
<tr>
<td>Headache*</td>
<td>15</td>
</tr>
<tr>
<td>Urinary Tract Infections*</td>
<td>9</td>
</tr>
<tr>
<td>Weight Gain*</td>
<td>7</td>
</tr>
<tr>
<td>Flatulence*</td>
<td>5</td>
</tr>
<tr>
<td>Herpes Zoster*</td>
<td>2</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

- Includes cutaneous, eczematous, hematochromatosis, injection site hematoma, portacaval hemostasis, vessel puncture site hematoma, increased tendency to bruising, cough, nausea
- Includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's disease, laryngitis
- Includes urinary tract infection, cystitis, urethritis, urinary tract infection bacterial, kidney infection, pyuria, bacteria, urological infection identified, nitrite urine present
- Includes weight increased, abnormal weight gain
- Includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Reactions: Anemia

In the two Phase 3 clinical studies, median time to onset of Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new stable nadir of 1.0 to 1.5 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.

Thrombocytopenia

In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 x 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimen. Discontinuation...
of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 × 10^9/L to 200 × 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 × 10^9/L (17% versus 7%). Neutropenia in the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematologic abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3/4 (%)</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31/1</td>
<td>11/0</td>
</tr>
<tr>
<td>Anemia</td>
<td>13/1</td>
<td>18/3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15/2</td>
<td>5/2</td>
</tr>
</tbody>
</table>

Additional Data from the Placebo-Controlled Study

- 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alamine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Polycythemia Vera in a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

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

<table>
<thead>
<tr>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15/3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10/3</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>12/2</td>
</tr>
<tr>
<td>Constipation</td>
<td>10/3</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>10/3</td>
</tr>
<tr>
<td>Nausea</td>
<td>10/3</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>6/3</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>6/3</td>
</tr>
</tbody>
</table>

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>58/0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10/1</td>
<td>0</td>
</tr>
<tr>
<td>Chemistry</td>
<td>23/1</td>
<td>1&lt;1</td>
</tr>
</tbody>
</table>

Acute Graft-versus-Host Disease: In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for aGVHD failing treatment with steroids and/or immunomodulatory drugs (see Clinical Studies (14.3) in Full Prescribing Information). The median duration of treatment with Jakafi was 46 days (range, 3-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 21% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

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

<table>
<thead>
<tr>
<th>Jakafi (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
</tr>
<tr>
<td>Infections (pathogen not specified)</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Viral infections</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worst grade during treatment</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>58/0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10/1</td>
</tr>
<tr>
<td>Chemistry</td>
<td>23/1</td>
</tr>
</tbody>
</table>

Table 7: Chronic Graft-versus-Host Disease: All-Grade (≥10%) and Grades 3-5 (≥3%) Nonhematologic Adverse Reactions Occurring in Patients in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

<table>
<thead>
<tr>
<th>Jakafi (N=165)</th>
<th>Best Available Therapy (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Infections (pathogen not specified)</td>
<td>45/15</td>
</tr>
<tr>
<td>Viral infections</td>
<td>25/5</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>13/1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>13/1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>15/3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>12/2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10/1</td>
</tr>
</tbody>
</table>

Table 8: Chronic Graft-versus-Host Disease: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Jakafi (N=158)</th>
<th>Best Available Therapy (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>40/8</td>
<td>35/7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27/12</td>
<td>29/13</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58/20</td>
<td>54/17</td>
</tr>
<tr>
<td>Chemistry</td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>88/10</td>
<td>85/8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>65/5</td>
<td>54/6</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>72/11</td>
<td>76/11</td>
</tr>
<tr>
<td>Glutamintransferase increased</td>
<td>81/41</td>
<td>75/38</td>
</tr>
<tr>
<td>Creatine increased</td>
<td>47/1</td>
<td>40/2</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>38/12</td>
<td>30/9</td>
</tr>
<tr>
<td>Elevated amylase</td>
<td>35/8</td>
<td>25/4</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS
Fluconazole Concomitant use of Jakafi with fluconazole increases rituximab exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information], which may increase the risk of exposure-related adverse reactions. Avoid concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily. Reduce the Jakafi dosage when used concomitantly with fluconazole doses of less than or equal to 200 mg [see Dosage and Administration (2.5) in Full Prescribing Information]. Strong CYP3A4 Inhibitors Concomitant use of Jakafi with strong CYP3A4 inhibitors increases rituximab exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information], which may increase the risk of exposure-related adverse reactions. Reduce the Jakafi dosage when used concomitantly with strong CYP3A4 inhibitors except in patients with g6PD or g6PDH [see Dosage and Administration (2.5) in Full Prescribing Information]. Strong CYP3A4 Inducers Concomitant use of Jakafi with strong CYP3A4 inducers may decrease rituximab exposure [see Clinical Pharmacology (12.3) in Full Prescribing Information], which may reduce efficacy of Jakafi. Monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS
Pregnancy: Risk Summary When pregnant rats and rabbits were administered rituximab during the period of organogenesis, adverse developmental outcomes occurred at doses of maternal toxicity [see Data]. There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated population is unknown. Advise women of reproductive potential to use effective contraceptive methods during and for at least 12 months after the last dose of Jakafi. Jakafi was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 5% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 5% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with rituximab and lactation through gestation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily).

Lactation: Risk Summary No data are available regarding the presence of rituximab in human milk, the effects on the breast fed child, or the effects on milk production. Rituximab and its metabolites were present in the milk of lactating rats and monkeys. Because many human lactating women are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. In lactating rats, animals had been administered a single dose of [14C]-labeled rituximab (50 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 3-fold the maternal plasma AUC. Additional analysis showed the presence of rituximab and several of its metabolites in milk, at all levels higher than those in maternal plasma.

Pediatric Use The safety and effectiveness of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients have not been established. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults [see Clinical Studies (14.3, 14.4) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. Safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents [see Clinical Studies (14.3, 14.4) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to < 17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m² twice daily in 28-day cycles with up to 6 patients per dose level. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults.

Juvenile Animal Toxicity Data Administration of rituximab to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of effects on bone development occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2 to 3-years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

Geriatric Use Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with g6PD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with g6PD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Renal Impairment Total exposure of rituximab and its active metabolites increased with moderate (CrCl 30 to 59 mL/min) and severe (CrCl 15 to 29 mL/min) renal impairment, and ESRD (CrCl less than 15 mL/min) on dialysis [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Modify Jakafi dosage as recommended [see Dosage and Administration (2.6) in Full Prescribing Information].

Ileal Impairment Exposure of rituximab increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information].
which could be magnifying the detrimental effects of tobacco. It would be interesting to see how the levels of radon, arsenic, lead, etc are contributing to possible underlying DNA damage, which could also be contributing to the increased prevalence of cancer, including lung cancer, in these areas.”

Brainson agreed: “I think that smoking is a driver but we can’t discount other possible causes including radon gas that can build up in houses—and radon has been shown to cause more adenocarcinoma and SCLCs. There are also other environmental exposures like indoor air pollution, coal mining, and exposure to heavy metals in the water. Those are all things that [individuals] here at the Markey Cancer Center are actively researching.”

The issue in Kentucky is an ongoing challenge for oncologists and their patients. But cancer centers are working to make connections with the patients most heavily impacted.

“There are still some barriers in the fact that we just need to get out to the rural communities and build trust with them so that they really see that Markey Cancer Center is a great place to go, as are any of the affiliated hospitals. We hope they choose us if they did have a lung cancer diagnosis. But that’s something that we’re just going to have to work out over time to make sure that we keep the conversation going with the more rural communities,” said Brainson.

Kentucky is not alone in battling high rates of lung cancer. Right behind Kentucky in the rankings are Alabama, Arkansas, Louisiana, Mississippi, Tennessee, and West Virginia.

Research shows that in the 15% to 20% of rural US regions, cancer mortality is consistently higher, compared with urban and suburban areas. Individuals in rural communities more often receive diagnoses in the later stages of disease; such areas have high cancer incidence rates overall. Multiple studies looking into causes of the disparity in rural America have cited issues such as poverty, lack of health insurance, and lack of access to primary or specialty care.9

REFERENCES
In modern medicine, electronic medical records (EMRs) have become ubiquitous, and for good reason. EMRs were initially devised in the 1980s and 1990s to improve quality and efficiency of health care delivery, improving processes that had been in place for decades and aiding both patients and providers.

Today’s EMRs allow providers to have accurate, up-to-date, and complete information, provide quicker access than a physical file, improve security and privacy, improve patient communication, enable safer prescriptions, and even cut costs. These platforms are being developed by technology start-ups, health care organizations, and hospitals, all to improve the way information is gathered, stored, and shared.

However, the mere existence of EMRs as a superior alternative to paper copies of patient records does not make them infallible. Despite the widespread use of EMRs, they have not fully lived up to their promise—and in some cases, their use has impaired the effectiveness of care delivery, especially among oncologists and other specialists.

I’ve taken a special interest in EMRs and their effectiveness. In addition to my own use of EMRs and conversations with my peers, I’ve written about the ways EMRs contribute to clinician burnout and even how it can alert providers when social determinants of health (SDOH) may put patients at more risk. My colleagues and I at Cardinal Health embarked on a survey about various trends and critical issues with EMRs in oncology care.

The abstract, which was presented at the 2021 American Society of Clinical Oncology Quality Care Symposium, discussed multiple deterrents that were efficient to use with current EMR systems, as well as essential information in the design of next-generation EMRs that will allow for the incorporation of aspects that are more useful to the end users.

Looking at the Responses
The objective was to identify barriers perceived by medical oncologists and hematologists in the way they utilize EMR software. The study also aimed to identify the factors associated with levels of satisfaction or dissatisfaction with current software.

We used a web-based survey to gauge satisfaction with current EMR software through a series of questions to physicians. Between January and April 2021, 369 geographically diverse participants from across the United States were invited to complete the survey. Responses were aggregated and analyzed using descriptive statistics.

Overall, 72% practice in a community setting and 47% identified as a hospital employee. Participants had an average 19 years of clinical experience and...
spend an average of 86% of their working time in direct patient care, seeing an average 17 patients per day on clinic days. Nearly all those surveyed (99%) use an EMR software of some kind at their practice, with Epic (45%) and OncoEMR (16%) being the most common.

**Clinician’s Attitudes About EMRs**

One of the main goals of the study was to establish the areas in which providers see value and effectiveness with their EMR software and in which areas they struggle or feel burdened by the systems with which they work on daily.

Overall, the study found that most appreciate their EMR software and are satisfied with its performance. At baseline, we asked participants to rank their current EMR software on a scale of “very satisfied” to “very dissatisfied,” and 66% of the participants were either “satisfied” or “very satisfied.” This is important because it indicates that EMRs are valued by clinicians.

We also wanted to investigate what made EMRs effective. When asked what the most useful aspects or features of their EMRs were, overwhelmingly, respondents said the availability of information, such as preloaded protocols, chemotherapy regimens and pathways (64%), and data access (64%). A smaller number of respondents also appreciated the availability of multiple access points, including remote access (37%) and a fast or easily navigated display (27%).

**Pain Points Associated With EMRs**

The study identified the challenges and frustrations associated with current software. We asked participants what their biggest pain points were with their current EMRs. Most participants (70%) said the “time-consuming” nature of their current EMR software was their biggest issue. This includes software requiring too many steps, or too many clicks, to achieve its functions. Nearly half of participants (45%) also said interoperability (eg, difficulty sharing information across institutions or other EMR software) was a pain point. A sizable number of respondents also noted the challenges of data entry issues (38%), such as difficulty entering clinical information, scheduling patient visits and reminders, or ordering multiple labs and poor workflow support (31%), which includes missing instructions and issues submitting chemotherapy orders or treatment pathways.

With these results, we can conclude that satisfaction with EMRs is generally positive among those surveyed, but there are multiple deterrents to the efficient use of current EMR systems. This information is essential in the design of a next-generation EMR (an intelligent medical records system) that would incorporate aspects most useful to clinicians, such as pathway access, preloaded information on cancer management, as well as ease of access and portability, and a user experience that minimizes clicks and reduces physician time with EMR.

**Why It Matters**

Across the board, we know clinicians want to spend more time with patients, but the reality is their time is often consumed with paperwork or documentation, such as EMRs.\(^4\)\(^5\)

However, we are facing the inflection point.

Last year, I wrote about burnout among community oncologists. For a study published in *JCO Oncology Practice*, my colleagues and I conducted web-based, paid surveys of US community oncologists/hematologists from September to November 2018.\(^6\)

Physicians were asked about frequency of burnout symptoms, drivers of work-related stress, and their perceptions on management of workload. We found plenty of evidence that proved EMRs could help.

In fact, EMR responsibilities caused moderate to excessive stress at work for 67% of physicians, with 79% of physicians working on EHRs outside of clinic hours. Unfortunately, most oncologists are experiencing burnout symptoms and require additional time beyond what is already allocated to complete their workload.

On top of the burnout, research is increasingly showing that SDOH-related factors affect cancer survivorship\(^*\) and that physicians need more time and mental space to fully understand not only their patients’ clinical conditions but also their socioeconomic conditions.

**What Comes Next?**

With the data gathered from this survey, we have a better understanding of what clinicians need and how we can address these issues moving forward.

The next-generation EMRs should be an intelligent medical record rather than just an electronic one. It should incorporate aspects that are most useful for the end users, such as efficiency, access, and availability. Such pain points should be further explored that could result in actionable upgrades to EMR design, leading to improved input processes, interoperability with other software, and ease of data entry.

These innovations could create a user experience that minimizes clicks and reduces physicians’ time using the EMR.

**REFERENCES**


Case-Based Peer Perspectives

IN CHOLANGIOCARCINOMA

Renowned opinion leaders provide insights on different case scenarios.

Q: When would you recommend biomarkers and molecular testing?
A: I discussed a few examples of targeted therapies finding their way into the landscape of cholangiocarcinoma. Therefore, molecular testing has become a paradigm for evaluation of patients with cholangiocarcinoma. A variety of targeted therapies have FDA approval in the setting as mentioned; ivosidenib, pemigatinib and others.

Case

Initial presentation
- A 75-year-old man presents with abdominal pain and weight loss.

Clinical workup
- History of hepatitis B infection more than 10 years ago and hypertension, which is controlled with medication
- Blood work reveals serum levels of CA 19-9 (1200 U/ml), bilirubin 1.5 mg/dL, alanine aminotransferase 250 U/L, aspartate aminotransferase 95 U/L
- MRI imaging shows multiple liver masses
- Histopathological examination identifies adenocarcinoma with primarily mucin-producing glands
- Patient is identified to have intrahepatic cholangiocarcinoma (ICCA).
- Complete blood count is unremarkable (absolute neutrophil count 3500/mm³, platelets 300,000/ml, hemoglobin 10.1 g/dL)
- ECOG performance score is 1 and the patient is in good health.
- Patient is referred to oncologists for next steps and is started on treatment with gemcitabine and cisplatin in June 2021.

CASE

September 2021
- Patient is experiencing grade 2-3 neutropenia and fatigue and the oncologist has adjusted the dose to reduce toxicities with chemotherapy.

Q: In screening and monitoring these patients, which factors should they be screened for and what imaging modalities would you recommend?
A: There is no standard or recommended screening strategy for cholangiocarcinoma. These patients are diagnosed based on their symptoms, even in the population with high risk for development of cholangiocarcinoma, such as primary biliary cirrhosis. Given the challenges and difficulties in identifying the cancer, it's not generally recommended to screen these patients. There is no imaging modality or laboratory tests that would identify these patients. I think the one thing that's very important is for patients who present with persistent symptoms like abdominal pain going on for month after month, it's important to not just assume that the abdominal pain is related to GERD [gastroesophageal reflux disease], or for a young female to assume it's related to IBS [irritable bowel syndrome]. We need to look radiographically to see if there are any tumors identified by imaging. I would say the best screening modality is paying attention to the symptoms that these patients present with. Look for early identification of the disease with the appropriate use of imaging in patients with persistent symptoms.

Q: Do you reflect on this patient's trajectory and, typically, what your clinic sees in patients with advanced or metastatic cholangiocarcinoma?
A: BARZI: Cholangiocarcinoma is a heterogeneous disease. We have patients who do well for a long time and those who decline very quickly. Predicting how a patient will do based on the information we have is, most of the time, very difficult. One thing is critical: these patients need to be followed very closely. Although radiographic assessment for definition of the progression is and should be standard of care, if we notice any significant decline in organ function or a patient's performance status and symptoms, it is reasonable to consider subsequent lines of therapy. Up until recently, cholangiocarcinoma did not have any established subsequent lines of therapy past gemcitabine and cisplatin. Although, over the past 2.5 to 3 years, we've had multiple trials that have shown active agents in subsequent lines of therapy. These include chemotherapy combinations such as FOLFOX [folinic acid, fluorouracil, oxaliplatin], which was studied in the ABC-06 [NCT01926236] trial, and more recently published, 5-FU [fluorouracil] and Onivyde [liposomal irinotecan] based on the NIFTY [NCT03524508] trial. Also, there are targeted therapies for selected populations, such as ivosidenib [Tilsovo], which is FDA-approved for patients with IDH mutations. In addition, there are agents that target FGFR alterations, such as pemigatinib [Pemazyre] and infibatinib [Truseltiq]. Given that the number of options for this patient population is expanding, it's important to identify the patients who are intolerant or not benefiting from their frontline therapy, and appropriately transition them in a timely manner to subsequent lines of therapy. This allows them to see the benefit of the drugs that they're not exposed to in the frontline setting.
inifratinib are examples of that. Other targeted therapies, although not FDA approved, do have data to support them, such as BRAF [inhibitors]. There are also tumor-agnostic therapies such as MSI [microsatellite instability] and NTRK fusions that, considered together, provide the rationale for looking for these changes in this patient population. The questions are when to test, what to test, what to look for in a test, and what platform of testing is the most appropriate? I do believe that in patients who are fit, up-front testing is the best strategy. Part of the reason for that is that there are clinical trials in the up-front setting that we may be able to get these patients on. However, the more important thing is that this can be a rapidly progressive disease with a rapid decline in the patient’s condition. If they’re discovered to have disease progression, the time that is spent to identify any marker in that window can potentially be detrimental to the patient condition and the opportunity for use of a targeted therapy. Therefore, earlier testing for better identification of the potential biomarkers for therapy is recommended in this patient population.

The other problem with this patient population is sometimes the biopsy specimen that we have on these patients is very small. I may submit tissue that I have that’s obtained through the diagnostic process, then the result I get is that the tissue is inadequate for NGS [next-generation sequencing] or any other molecular testing that we are interested in. If the patients are in good shape, that provides the opportunity for repeat biopsy, better testing, and gives us a window of opportunity to identify the right patient for the right treatment. The other question is what kind of testing should we do? I know many of us in the oncology community have been users of next-generation sequencing, which in my opinion is an appropriate platform to use in this patient population given the multitude of the targets. The fact that tissue may not be adequate to do test by test, the thing that we must be careful about is we have to look at the results of the molecular or NGS testing very carefully. Usually when we get the results, a summary of the findings are on the front page.

The real question is not what was found on the tissue, but also what wasn’t found. Usually there is a table that says whether the tissue was inadequate, or the amount and the quantity of DNA, or the technology was inadequate for testing specific targets. That’s important to know. An example is that if you’re looking for FGF2 fusions, which are the biomarker for inifratinib and pemigatinib, and you look back and it says they could not verify the presence of FGF2 fusions, then not seeing that result on the front page doesn’t mean the patient doesn’t have it. It only means we need to dig deeper to identify these patients and be certain that a negative result is a true negative result. Another thing is the use of liquid biopsies and whether there’s a justification for using liquid biopsy in this setting. Although liquid biopsies are good and well validated for mutations, their ability to detect other genomic alterations, such as fusions or rearrangements, is very limited. Relevant to the FGF2 fusions, there was an abstract that was presented at ASCO [American Society of Clinical Oncology annual meeting] 2019 that looked at the Guardant360 test for detection of an FGF2 alteration in the urethral cancer population.\(^4\) The Guardant360 test was correlated with the tissue testing. Only 25% of the patients who on the tissue had FGF2 alterations were identified to have FGF2 fusions by liquid biopsies.

Although these tests are evolving and are getting better, purely relying on liquid biopsies for this unique genomic alteration should be avoided. The other caveat with the liquid biopsies is the timing of the test. Testing the patient at the time of their best response to therapy isn’t optimum for identifying the cell-free DNA. You can imagine that if a patient had responded to therapy, the shedding of the tumor or the volume of the DNA in the circulating blood is less; therefore, the likelihood of finding something that would be guiding the treatment goes down. To summarize, I think NGS is the standard testing. Testing should be done on the tissue, and liquid biopsies should be avoided for the most part. If for any reason there is a patient for whom it’s difficult to obtain a repeat biopsy and we’re relying on liquid biopsy, we should do the testing at a time when the patient is progressing or has maximum quantity of the tumor to reduce the chance of not detecting adequate DNA, and, as a result, the changes we’re looking for to guide our therapy.

How do you choose between first-line treatments for advanced/metastatic cholangiocarcinoma?

For advanced metastatic cholangiocarcinoma, the standard of care is gemcitabine and cisplatin based on the ABC-02 [NCT00262769]\(^7\) trial, which was published almost 12 or 13 years ago. There are 2 trials that are worth mentioning. One is the SWOG-S1815 [NCT02392637]\(^7\) trial and the PI [principal investigator] is [Rachna] Shroff, [MD]. This looked at triplet chemotherapies, where they added Abraxane [nab-paclitaxel] to gemcitabine-cisplatin. Everybody’s eagerly waiting for the results of the trial. On October 25, [2021], there was a press release from AstraZeneca reporting that the TOPAZ [NCT03875235]\(^7\) trial, which looked at gemcitabine-cisplatin vs gemcitabine-cisplatin in combination with durvulumab [Imfinzi], had met its primary end point for improvement in overall survival. It was a positive trial. Although I haven’t seen any of the results, I think it is very encouraging that maybe immunotherapy is going to be a therapeutic option for the frontline setting of patients with cholangiocarcinoma. One thing that we must keep in mind is that in many of these frontline therapies, whether we look at ABC-02 or TOPAZ, or many other trials, there is a mix of cholangiocarcinoma and gallbladder cancer. In other words, these are trials for biliary tract cancer; therefore, gallbladder cancer is also included in the trial population. It’s important to know those caveats and minor differences between these trials. There’s another trial with results [that will be available] very soon. That’s KEYNOTE-966 [NCT04003636]\(^7\), which looked at the combination of pembrolizumab [Keytruda] with gemcitabine and cisplatin. I am guessing if the…trial was positive, that this one hopefully will be positive, too, so the results of that one are eagerly awaited.

The gentleman in this case received an excellent therapy. I think gemcitabine-cisplatin is the up-front therapy in this patient population. This patient had a bilirubin level under 2 [mg/dL]; I know we are cautious about using gemcitabine in patients with high bilirubin. He did have a performance status of 1, all of which are meeting the requirement for offering this therapy. It’s not the easiest therapy; it does have adverse effects like any other chemotherapy that we offer. I think the oncologist is doing a fabulous job monitoring the patient and adjusting based on the toxicities that were reported, which included fatigue and neutropenia. I think the treatment was very appropriate. The data I shared for gemcitabine-cisplatin and durvulumab are very new. It wasn’t available at the time this patient was diagnosed, and it’s not a standard of care at this time. We’re just seeing a glimpse into the data, however, yes, this gentleman [received] appropriate therapy.

Can you talk about importance of enrolling patients in clinical trials for cholangiocarcinoma?

CONTINUED ON PAGE 89 ✤
LENVIMA + everolimus is the only TKI-mTOR inhibitor combination following anti-angiogenic therapy in advanced RCC\textsuperscript{1,2}

**INDICATION**
LENVIMA is indicated in combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

**SELECTED SAFETY INFORMATION**

**Warnings and Precautions**

**Hypertension.** In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

**Cardiac Dysfunction.** Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Arterial Thromboembolic Events.** Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials. Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

**Hepatotoxicity.** Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Renal Failure or Impairment.** Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus-treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

**Proteinuria.** In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Diarrhea.** Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Diabetes Mellitus.** In DTC and HCC, diabetes mellitus occurred in 21% and 27%, respectively. In RCC, diabetes mellitus occurred in 14% of patients. Commonly reported hyperglycemic reactions included elevated fasting glucose and glycosylated hemoglobin.

**Hyperglycemia.** Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.
14.6-month median PFS: with LENVIMA + everolimus vs everolimus alone¹

- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm¹
  - 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus
  - Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus

The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs with an observed HR of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm¹

Study 205 randomized 153 patients with advanced or metastatic renal cell carcinoma who had previously received anti-angiogenic therapy 1:1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (<10 g/dL vs ≥10 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other efficacy outcome measures included overall survival and objective response rate¹

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont’d)

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In RCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA–treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Visit www.LENVIMA.com/hcp to learn more

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SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont’d)

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA–treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA–treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal cerebral artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA–treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA–treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA–treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ. Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

ADVERSE REACTIONS

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus–treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspepsia (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diastolic (6%), vomiting (6%), and dyspepsia (5%). Adverse reactions led to dose reductions or interruption in 86% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (Clcr 60-89 mL/min) or moderate (Clcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC (endometrial carcinoma) and severe (Clcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

Please see Brief Summary on the following pages.

LENVIMA® (lenvatinib) capsules BRIEF SUMMARY – See package insert for full prescribing information.

INDICATIONS AND USAGE
LENVIMA is a kinase inhibitor that is indicated:
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SPECIAL SITUATIONS
• In patients receiving LENVIMA 18 mg orally once daily with everolimus in SELECT (DTC), hypocalcemia was managed by decreasing the dose of everolimus and withholding LENVIMA. Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

CONTRAINDICATIONS
• Do not administer LENVIMA with pembrolizumab as it will result in an increased risk of immune-related adverse reactions.

DRUG INTERACTIONS
• PLASMA LEVELS: Monitor LENVIMA and pembrolizumab plasma levels prior to initiating LENVIMA and during LENVIMA treatment. Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

ADVERSE REACTIONS
Table 1: Recommended Dosage Modifications for LENVIMA for Adverse Reactions

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<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dose Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Grade 3</td>
<td>Withhold for 2-4 weeks; then resume or reduce depending on severity and persistence of hypertension.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Osteonecrosis of the Jaw</td>
<td>Grade 3</td>
<td>Withhold until improved to Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of osteonecrosis.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Hemolytic Uremic Syndrome</td>
<td>Grade 3</td>
<td>Withhold until improved to Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of hemolytic uremic syndrome.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Renal Failure or Impairment</td>
<td>Grade 3</td>
<td>Withhold until improved to Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of renal failure or impairment.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Grade 2</td>
<td>Withhold if urine protein ≥0.5 g/L and Grade 3-5 proteinuria.</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Withhold if urine protein ≥1.0 g/L and Grade 3-5 proteinuria.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of proteinuria.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>Grade 3</td>
<td>Withhold until fully resolved.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of diabetic nephropathy.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>GT Proliferation</td>
<td>Grade 3</td>
<td>Withhold if greater than or equal to 30% increase from baseline.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of GT proliferation.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Grade 3</td>
<td>Withhold until improved to Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of myelosuppression.</td>
</tr>
<tr>
<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Grade 3</td>
<td>Withhold until improved to Grade 1.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Resume at a reduced dose or discontinue depending on severity and persistence of other adverse reactions.</td>
</tr>
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<td></td>
<td>Grade 5</td>
<td>Permanently discontinue.</td>
</tr>
</tbody>
</table>

| National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 |

Table 2: Recommended Dosage Reductions of LENVIMA for Adverse Reactions

<table>
<thead>
<tr>
<th>Modification</th>
<th>First Doseage Reduction</th>
<th>Second Doseage Reduction</th>
<th>Third Doseage Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>8 mg daily</td>
<td>4 mg daily</td>
<td>2 mg daily</td>
</tr>
<tr>
<td>Duration</td>
<td>Day 1 to Day 7</td>
<td>Day 8 to Day 21</td>
<td>Day 22 to Day 28</td>
</tr>
</tbody>
</table>

Note: Dose modifications should be based on the patient’s ability to tolerate LENVIMA. Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity.

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DRUG INTERACTIONS
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ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere in the labeling:
• Hypertension
• Cardiac Dysfunction
• Arterial Thromboembolic Events
• Reversible Posterior Leukoencephalopathy Syndrome
• Hemorrhage
• Diarrhea
• Fistula Formation and Gastrointestinal Perforation

SELECTED SAFETY INFORMATION
LENVIMA® is a registered trademark used by Eisai Inc. under license from Eisai R&D Management Co., Ltd.
The following laboratory abnormalities (all Grades) occurred in >5% of LENVIMA-treated patients and at a rate that was two-fold or higher than that in patients who received placebo:

- Laboratory Abnormalities (%)

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<tr>
<th>Adverse Reaction</th>
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<tbody>
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<td>Renal and Urinary</td>
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<td>N=131</td>
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<td>Hyponatremia</td>
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Clinical adverse reactions occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of ≤2% or only sporadically reported, including fatal reports, are summarized in the Table 4 below.

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<td>17 1</td>
</tr>
<tr>
<td>Hypnotic</td>
<td>23 1</td>
<td>16 1</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>23 1</td>
<td>16 1</td>
</tr>
</tbody>
</table>
In Table 8, Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA with everolimus arm are presented.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LENVIMA 20 mg in combination with Pembrolizumab 200 mg</th>
<th>Sorafenib 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13</td>
<td>17.5</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
<td>18.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18</td>
<td>28.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>1.7</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>10</td>
<td>11.1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>16.1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>14</td>
<td>17.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8</td>
<td>9.9</td>
</tr>
<tr>
<td>Renal failure event</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2</td>
<td>6.4</td>
</tr>
<tr>
<td>Muscle/cachexia and Toxicity</td>
<td>8</td>
<td>14.7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13</td>
<td>21.9</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>37.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>49.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>25.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>22.7</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>13</td>
<td>19.5</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>14</td>
<td>21.6</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased weight</td>
<td>30</td>
<td>43.8</td>
</tr>
<tr>
<td>Increased weight</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>11</td>
<td>16.5</td>
</tr>
<tr>
<td>Increased urea</td>
<td>10</td>
<td>14.9</td>
</tr>
<tr>
<td>Increased sodium</td>
<td>9</td>
<td>13.5</td>
</tr>
<tr>
<td>Increased phosphorus</td>
<td>8</td>
<td>11.7</td>
</tr>
<tr>
<td>Increased uric acid</td>
<td>12</td>
<td>17.6</td>
</tr>
<tr>
<td>Increased cholesterol</td>
<td>10</td>
<td>14.8</td>
</tr>
<tr>
<td>Dyspepsia/ Gastropathy</td>
<td>13</td>
<td>19.6</td>
</tr>
<tr>
<td>Abnormal lipase</td>
<td>14</td>
<td>21.6</td>
</tr>
<tr>
<td>Hemothermic events</td>
<td>23</td>
<td>34.4</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep problems</td>
<td>10</td>
<td>14.8</td>
</tr>
<tr>
<td>Vascular</td>
<td>7</td>
<td>10.3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>15</td>
<td>22.4</td>
</tr>
<tr>
<td>No adverse reaction</td>
<td>60</td>
<td>90.2</td>
</tr>
</tbody>
</table>

Table 9: Adverse Reactions Occurring in ≥1% of Patients in the LENVIMA Arm in Study 205 (RCC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LENVIMA 20 mg with Everolimus N=62</th>
<th>Sorafenib N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia/Gastro-esophageal reflux</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Increased urea</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Increased sodium</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Increased phosphorus</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Increased uric acid</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Increased cholesterol</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>No adverse reaction</td>
<td>47</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 8: Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA arm are presented.

Hepatocellular Carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomized 811 patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=406) or sorafenib (n=405). The dose of LENVIMA was 20 mg orally once daily for patients with a baseline body weight of ≥60 kg and 10 mg orally once daily for patients with a baseline body weight of <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was climb to 45% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 406 patients who received LENVIMA in REFLECT, the median age was 63 years, 85% were men, 28% were White and 70% were Asian. The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-planar erythrodysesthesia syndrome, pyrexia, dysphonia, hemoptysis, arterial events, hypophosphatemia, and anemia. The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), anemia (5%), and decreased appetite (7%). Adverse reactions led to dose reduction or interruption in 82% of patients receiving LENVIMA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-planar erythrodysesthesia syndrome (5%). Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions leading to discontinuation of LENVIMA were fatigue (7%), hepatic encephalopathy (3%), hypophosphatemia (3%), and hepatic failure (2%). Table 9 summarizes the adverse reactions that occurred in ≥1% of patients receiving LENVIMA in REFLECT. REFLECT was not designed to demonstrate a statistically significant difference in adverse reaction rates in LENVIMA as compared to sorafenib, for any specified adverse reaction listed in Table 9.
Dose interruptions of LENVIMA due to an adverse reaction occurred in 56% of these patients. The most common (≥2%) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (9%), decreased appetite (9%), vomiting (9%), increased aspartate aminotransferase (5%), fatigue (5%), nausea (5%), abdominal pain (2%), weight decreased (2%), urinary tract infection (2%), increased platelet count (2%), decreased sodium (2%), and hypercholesterolemia (2%).

Table 11 and 12 summarize adverse reactions and laboratory abnormalities, respectively, in patients receiving LENVIMA in Study 308.

Table 11: Adverse Reactions in ≥20% of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction</strong></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory abnormality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Laboratory Abnormalities Altered from Baseline Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients Receiving LENVIMA plus Pembrolizumab in Study 309 (EC)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

**Pregnancy**

Risk Summary

Based on its mechanism of action and data from animal reproductive studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. These are not available human data informing the drug-associated risk. Advise pregnant women of the potential risk to the 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

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses ≥0.3 mg/kg [approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)] in pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (periorbital edema and tail) and internal abnormalities. Liver and skeletal abnormalities. Trophic (day 18) postimplantation loss was observed at 1.0 mg/kg [approximately 0.5 times the recommended clinical dose of 24 mg based on BSA].

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), exsanguination (intracerebral subdural and intracardiac), skeletal anomalies at doses greater than or equal to 0.1 mg/kg [approximately 0.03 times the recommended clinical dose of 24 mg based on BSA]. At the 0.05 mg/kg dose, increased postimplantation loss, including 1 fetal death, was also observed. Lenvatinib was not administered to rabbits, resulting in late abortions in approximately 50% to 80% of the rabbits treated at a dose level of 0.5 mg/kg/day [approximately 0.3 times the recommended clinical dose of 24 mg based on BSA].

**Lactation**

Risk Summary

It is not known whether LENVIMA is present in human milk; however, lenvatinib and its metabolites are excreted in rat milk concentrations higher than those in maternal plasma. Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment with LENVIMA and for at least 1 week after the last dose.

**Data**

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher than radioactivity in the milk compared to maternal plasma.

**Females and Males of Reproductive Potential**

**Pregnancy Testing**

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

**Fertility**

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

**Infertility**

LENVIMA may impair fertility in males and females of reproductive potential.

**Pediatric Use**

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

**Adverse Drug Reactions**

**Dose-Intensive**

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.

**Drug Interactions**

**Dose Adjustments**

In general, lenvatinib is metabolized by CYP3A4 and should be coadministered with CYP3A4 inhibitors with caution.

**Drug Interactions**

**Dose Adjustments**

In general, lenvatinib is metabolized by CYP3A4 and should be coadministered with CYP3A4 inhibitors with caution.
**Case-Based Peer Perspectives in Cholangiocarcinoma**

Renowned opinion leaders provide insights on different case scenarios.

**Q:** Can you discuss pemigatinib and infgratinib in the second line?

**A:** Pemigatinib and infgratinib have FDA approval for second and subsequent lines of therapy in patients with cholangiocarcinoma with FGFR2 fusions or alterations. For both drugs, the approval is based on a single-arm study. Pemigatinib was looked at in a study with 146 patients, 108 of them having an FGFR fusion. Pemigatinib had a response rate of 36% and a very prolonged duration of response of more than 6 months in this patient population; that’s an even bigger reason to be careful about the toxicities. I would go back to the response rate of these agents; both these agents have a very respectable response rate. In fact, what makes it very interesting is when we look at the first-line therapy, which is gemcitabine and cisplatin, the response rate is 28%. Then we look at the response rate in the second-line setting, and we see a rate in the same range as the first-line setting. That to me in the oncology community is impressive. What we know across the tumor types, as we go through the lines of therapy, is the response rate goes down and the duration of response goes down. The fact that we see these impressive responses in the second-line setting in this population speaks to the importance of this target for this tumor type. It falls on us as oncologists to not miss any patient who would have a chance to be treated appropriately with these agents.

Both infgratinib and pemigatinib are FDA approved and have class-related toxicities. Those include hyperphosphatemia, skin-related toxicities, and ocular toxicities. There are several ocular toxicities, including dry eye, which is the most common ocular toxicity. However, they’re also associated with pigmentation in the retina, which is very similar to the MEK inhibitors; many oncologists are familiar with MEK inhibitors from other diseases or other settings. The 1 important thing for these patients is to do an ophthalmological examination before initiating the therapy, and then at 1 month. If there are no issues at 3 months, then continue every 3 months with an ophthalmological examination. The dry eye can be bothersome to these patients, and consideration of supportive measures, such as artificial tears, are justified. If the dry eye is very severe, working with an ophthalmologist to offer other prescriptions to help manage these toxicities is critical.

The other class-effect toxicity is hyperphosphatemia. As oncologists we are not used to hyperphosphatemia; it is something that’s bread and butter for nephrologists dealing with patients with end-stage renal disease, but it’s not common for us in our field. This class of drugs does result in significant hyperphosphatemia. The development of hyperphosphatemia is early, usually within the first 2 to 3 weeks. It’s important to...
 وضع نظريات الأصدقاء المعتنقات

في الذين مصابين بسرطان الأغازه المالتيني، فهم الأصدقاء المعتنقات يتضمنون ملاحظات على أسئلة مختلفة.

كأسُلة يُعرف**: Ivosidenib can be used for IDH mutations. Can you talk about where it’s being used based on its efficacy and safety profiles?

أجوبة: Ivosidenib was also FDA approved this year for patients with cholangiocarcinoma and an IDH mutation. There was a randomized study [NCT02989857; FIGURE] looking at ivosidenib vs placebo, allowing the patients on placebo to be switched over to ivosidenib. It showed an improvement in the PFS [progression-free survival], which was the basis for FDA approval. In the control arm, the PFS was 1.4 months, and in the ivosidenib arm the PFS was 2.7 months with a hazard ratio of 0.37, and a significant P value. Although numerically it's a small improvement, it is a very respectable hazard ratio of 0.37, so I think it is an active drug. It is an oral agent.

The 1 thing about the drug that’s very interesting is one of the most common toxicities is ascites. However, when you look at the trial, the placebo arm experienced almost as much ascites as the treatment arm. Is this molecular change, which is an IDH mutation, potentially resulting in more peritoneal involvement in ascites than other tumor types? We do not know the answer. But the important thing is careful attention to management of ascites in this patient population. The drug is also associated with nausea, vomiting, diarrhea, and loss of taste and appetite. Those are toxicities that as oncologists we feel more familiar with and more comfortable managing them. However, one cannot argue with the fact that we now have a targeted drug for patients with IDH mutations. Testing is the only way you’re going to find these patients with these molecular alterations.

Q2: Can you elaborate on any second-and subsequent-line agents and immunotherapy combinations?

A2: There are good chemotherapy combinations in this patient population. We talked about FOLFOX based on the ABC-06 trial, and we talked about 5-FU and Onivyde based on the NIFTY trial. There are targeted therapies for patients we are identifying, and in those who are MSI-high, pembrolizumab remains a recommended second-line therapy in this patient population. Outside of that, although there are some smaller studies and a recommendation by NCCN [National Comprehensive Cancer Network] to consider immunotherapy in subsequent lines of therapy, I would say I don’t have any high-quality data to strongly recommend immunotherapy. I think we have very good chemotherapy options that have shown efficacy in trials and very good targeted therapy options. If you’re thinking about immunotherapy, we should see trials that are evaluating immunotherapy in second and subsequent lines of therapy. Additionally, if immunotherapy makes its way to the frontline setting and if patients are all potentially exposed to immunotherapy in the frontline setting, the role of this treatment in subsequent lines of therapy is going to go away. Immunotherapy in the second and subsequent lines of therapy for cholangiocarcinoma is not high on my list for most patients.

I would say cholangiocarcinoma is a mysterious disease. Patients present with liver metastatic disease, but a patient with colon cancer would present with liver metastatic disease, so appropriate workup to make sure this is truly cholangiocarcinoma is important.

If a patient hasn’t had a colonoscopy, considering colonoscopy and EGD [esophagogastroduodenoscopy] is important. There are some data that cholangiocarcinoma, and especially intrahepatic cholangiocarcinoma incidence, is rising, but it is believed that the rise is based on a better classification of tumors of unknown primary to cholangiocarcinoma. My general advice is if you see somebody with liver lesions, and you do a biopsy and it comes back adenocarcinoma, hepatobiliary primary, that is not necessarily a pancreatic cancer if you don’t see anything in the pancreas. That’s an important consideration because for the pancreas, FOLFIRINOX [folinic acid, fluorouracil, irinotecan, oxaliplatin] is a standard therapy. However, in a recently published study, FOLFIRINOX is actually not a good therapy for cholangiocarcinoma. We must be careful to label these patient cases appropriately and make sure we rule out common diseases such as colon cancer. And again, for a biopsy of the liver that reads as hepatobiliary malignancy, if you don’t see any pancreatic cancer or pancreatic lesions, think about cholangiocarcinoma. The treatment paradigms are very different.

Next, I would say don’t forget the molecular testing in this disease. This disease now has targeted therapies that are FDA approved. There are also many trials that are ongoing, targeted therapies that have good data behind them although they don’t have FDA approval, and those treatments are listed in the NCCN guidelines. As oncologists, our most important job is to label these cases appropriately, do not mislabel a patient with cholangiocarcinoma as having pancreatic cancer, and do not label them as cancer of unknown primary. It is our responsibility to label them appropriately, and it is on us to do appropriate and timely testing for identification of biomarkers. It’s on us to appropriately transition them from 1 line of therapy to another and to not miss the opportunity for the patient to get exposed to an effective therapy that can control their disease for a long time.
FIGURE. PATIENT DISPOSITION FOR TRIAL NCT02989857 eastside.

- 230 patients assessed for eligibility*
- 44 excluded for screening failure
- 1 patient still being screened at data cutoff
- 185 randomly assigned

- 124 patients allocated to receive ivosidenib at 500 mg once daily
  - 121 were treated
  - 3 were not treated due to elevated total bilirubin, clinical decompensation, and not meeting eligibility criteria

- 61 patients allocated to receive placebo
  - 59 treated
  - 2 not treated owing to health deterioration

- 8 on treatment*
- 51 discontinued treatment
  - 44 progressive disease
  - 4 adverse event
  - 2 withdrawal by participant
  - 1 withdrawal of consent

- 35 crossed over to receive ivosidenib (crossover analysis set)
  - 5 received ivosidenib
  - 30 discontinued treatment
  - 25 progressive disease
  - 2 adverse event
  - 2 physician decision
  - 1 withdrawal of consent

- 71 on study*
- 53 discontinued study
  - 47 death
  - 5 withdrawal of consent
  - 1 lost to follow-up

- 124 ITT analysis set
  - 121 safety analysis set
  - 3 patients excluded, did not receive study drug

- 27 on study*
- 34 discontinued study
  - 27 death
  - 7 withdrawal of consent

- 124 ITT analysis set
  - 59 safety analysis set
  - 2 patients excluded, did not receive study drug

*As of data cut off, January 31, 2019.

**As of data cut off, January 31, 2019.
PODCAST PREVIEW:
Cabazitaxel Shows Favorable Results But Treatment Concerns Remain
By Will Pizii

In Season 2, episode 9 of “Targeted Talks,” Sandy Srinivas, MD, a medical oncologist and professor of medicine (oncology) and urology at Stanford Health Care in California, and Nicholas J. Vogelzang, MD, FASCO, FACP, chairman of medical oncology at the Comprehensive Cancer Centers in Las Vegas, Nevada, discuss the optimal sequencing of therapies for a specific patient with metastatic castration-resistant prostate cancer (mCRPC).

The initial treatment for the 75-year-old patient was external beam radiation and androgen deprivation therapy for a period of 18 months. This strategy was selected based on the clinical work-up of the patient, which showed a prostate-specific antigen (PSA) level of 32.6 ng/mL, a Gleason score of 4 + 4 in the fourth grade group, and a negative bone and abdominal pelvic CT scan.

Srinivas and Vogelzang provided their expert opinions on frontline therapy for the patient, along with advice on how to choose between chemotherapy and androgen receptor (AR)-targeted therapy, how to intervene if the patient progresses, and how to mitigate toxicities.

Several studies were mentioned to support each physician’s therapy choices for the patient. Most notably, the CARD trial (NCT02485691) that evaluated cabazitaxel (Jevtana) vs AR-targeted therapy in patients with mCRPC previously treated with docetaxel (Taxotere) or quickly failed on AR-targeted therapy.

Below is an excerpted transcript of the podcast discussion.

Srinivas: How do you choose between chemotherapy and an AR-targeted drug? This patient started enzalutamide [Xtandi] at the standard dose of 116 mg per day. His PSA came down as low as 3.9 [ng/mL] 4 months after starting enzalutamide. Unfortunately, after 8 months, he had progression and his PSA increased to 60 [ng/mL]. He had imaging studies that showed both progression in his lymph nodes and bones, but he was asymptomatic. He started on docetaxel at the standard dose of 75/m² given every 3 weeks, along with prednisone. After 6 cycles of docetaxel, he developed neuropathy, docetaxel was held, and he was given a little chemotherapy break. He came back 3 months later but has a rising PSA and some new symptoms with back pain. What are you most likely to recommend now that the patient is progressing? Would you consider [abiraterone (Zytiga) and prednisone], or would you go with cabazitaxel or do radium? Is this the time to look at [microsatellite instability] and somatic mutations, or would you have an alternative?

Vogelzang: The study from [Dr] Kim Chi was very definitive. The response rate to enzalutamide after enzalutamide failure when [patients are] on abiraterone [plus] prednisone was minuscule. [Patients] don’t respond. Therefore, you really shouldn’t bother. You can try other nonsteroidal [treatments], [such as] apalutamide [Erleada], but it hasn’t been well studied. Potentially, you would have some benefit with apalutamide after enzalutamide, but generally, based on Kim Chi’s study and the CARD study, we would recommend docetaxel, cabazitaxel, or radium. If you find an MSI defect or a DNA defect, then go down that path.

Srinivas: The CARD trial is a phase 4 trial looking at cabazitaxel vs an AR-targeted agent. [There were] 255 patients [in the study]. All patients had CRPC who had progressed less than 12 months on a prior AR-targeted drug. It’s a 1:1 randomization. The [primary] end point is imaging-based progression-free survival [PFS]. The key secondary end points are overall survival, PSA response, tumor response, pain response, time to symptomatic...
skeletal-related events, and quality-of-life metrics. There are some stratification factors based on ECOG: time to progression on prior AR-targeted therapy and timing of AR before or after docetaxel. [In the study, 129 patients received] cabazitaxel vs the alternate AR at 126 [patients]. [Over] one-third were patients older than 75. This was a good mix, with almost 20% having a visceral disease. Most of these patients had progression and radiographic progression. One-third of patients had M1 disease at diagnosis. A very small fraction received either docetaxel or abiraterone for hormone-sensitive disease. If you look at the prior AR-targeted therapy, 43% received abiraterone and 55% received enzalutamide coming into the cabazitaxel arm.

The median duration of the prior AR was quite short at 7.6 months. The Kaplan-Meier analysis, which was positive for the imaging-based PFS end point for patients, was in favor of cabazitaxel at 8 months compared with the AR-targeted therapy at 3.7 months. The hazard ratio was 0.54 with a statistical P value. The trial’s preplanned subgroups favored cabazitaxel compared with the AR-targeted drug. The hazard ratios remain somewhere between 50 and 70. It’s a small trial but did have an improvement. The radiographic difference favored cabazitaxel at 13.6 vs the alternate AR at 11. Hazard ratio of 0.6, with a P value that was significant. PFS again favored cabazitaxel. A metric that is important to our patients is skeletal-related events, which also favored cabazitaxel. Most of the end points favored chemotherapy over the alternate AR-targeted drug.

What about quality of life? I think all these trials now show this. It appears that the overall quality of life favors chemotherapy over hormonal therapy, especially as far as the pain scale, it’s even statistically significant, favoring chemotherapy. I thought the CARD trial was what we’ve been doing in this practice for a while, knowing that there is significant cross resistance. What is your opinion on the CARD trial?

VOGELZANG: I’ve had a few people tell me they’re nervous about the Jevtana toxicities, with cabazitaxel being a dosage of 25 mg/m², and you have to give it with granulocyte colony-stimulating factor [G-CSF]. I don’t use that dose. I use 20 mg/m², and I generally don’t give G-CSF. The other thing some people have said is, “How can [it] be that abiraterone and enzalutamide caused increased risk of death?” I think it’s just a coding issue—that there were people who progressed rapidly. But the reality is that this is very concordant with what Dr Kim Chi’s data showed, namely that when you go to a second AR inhibitor agent, you don’t get much value of it. Therefore, disease can be rather explosive. Those are 2 things I’ve heard in my conferences with treating doctors about this trial.

REFERENCES

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