GI Cancer Expert Sets His Sights on the Next Generation

Peering Exchange
Long-term Data for CDK4/6 Inhibitors Solidify Role in First-line HR+/HER2-
Breast Cancer

Tumor Agnostic Role of TMB Faces Challenges

Conference Highlights
World GI
Updates in CRC, esophageal cancer, HCC, biliary tract cancer, and more

Clinical Perspectives
Steven V. Liu, MD; and Neal E. Ready, MD, PhD,
Discuss Long-term Treatment Outcomes With Dual Checkpoint Blockade in NSCLC

Weijing Sun, MD, FACP

Barbara Ann Karmanos Cancer Institute
CAR T-Cell Therapy Establishes Prominent Role Across Hematologic Malignancies
By Abhinav Deol, MD

OncLive.com
Bringing the Global Oncology Community Together
**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/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 the 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.
In the PRIMA trial:
More than 2X PFS vs placebo in HRd PATIENTS\textsuperscript{1,2}

**Study Design\textsuperscript{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%).

**Please see Brief Summary on the following pages.**

**References:**

CI = confidence interval; CR = complete response; HR = hazard ratio; PR = partial response.

Visit ZEJULAHCP.COM to explore the PRIMA data

Trademarks are property of their respective owners.

©2022 GSK or licensor.

NRPJRNA220001 March 2022
Produced in USA.
ZEJULA is indicated for the treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

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

5.3 Hypertension and Cardiovascular Effects

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

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 15 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

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

In QUADRA, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 138 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Consider monitoring 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 Prior 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 seizures, altered mental status, visual disturbance, or cortical blandness, 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 reinstituting ZEJULA in patients previously experiencing PRES is not known.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) of full prescribing information). ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted in niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraceptive during treatment and for 6 months after the last dose of ZEJULA (see Use in Specific Populations (8.1, 8.4) of full prescribing information).

5.6 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

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

6. ADVERSE REACTIONS

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

• MDSD/AML (see Warnings and Precautions (5.1))
• Bone marrow suppression (see Warnings and Precautions (5.2))
• Hypertension and cardiovascular effects (see Warnings and Precautions (5.3))
• Posterior reversible encephalopathy syndrome (see Warnings and Precautions (5.4))

6.1 Clinical Trials Experience

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

The most common adverse reactions of all grades in >10% of 1,314 patients who received ZEJULA in the placebo-controlled Phase III trials, NOVA, and QUADRA trials were nausea (85%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (35%), 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 (7%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hyperglycemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with 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 29 months).

All Patients Receiving ZEJULA in PRIMA

Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in ≥2% of patients were thrombocytopenia (15%), anemia (16%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in <1% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 85% of patients, most frequently from thrombocytopenia (56%), anemia (53%), and neutropenia (20%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (n=244)</td>
<td>Placebo (n=484)</td>
<td>ZEJULA (n=244)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Muscle/skeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle/skeletal pain</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.

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

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

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

- Includes neutropenia, neutropenic infection, neutropenic sepsis, and febrile neutropenia.
- Includes leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.
- Includes blood creatinine increased, acute kidney injury, renal failure, and blood creatine increased.
No fatal adverse reactions occurred in 27% of patients receiving ZEJULA. Among patients who received ZEJULA, serious adverse reactions occurred in 25% of patients treated with ZEJULA in PRIMA. Adverse reactions led to dose reduction or interruption in 73% of patients treated with ZEJULA in NOVA. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in 22% 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 (15%).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>87 66 29 1</td>
<td>87 66 29 1</td>
<td>87 66 29 1</td>
<td>87 66 29 1</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74 13 37 0</td>
<td>74 13 37 0</td>
<td>74 13 37 0</td>
<td>74 13 37 0</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71 36 9 0</td>
<td>71 36 9 0</td>
<td>71 36 9 0</td>
<td>71 36 9 0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>65 57 3 3</td>
<td>65 57 3 3</td>
<td>65 57 3 3</td>
<td>65 57 3 3</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66 25 23 1</td>
<td>66 25 23 1</td>
<td>66 25 23 1</td>
<td>66 25 23 1</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51 29 7 3</td>
<td>51 29 7 3</td>
<td>51 29 7 3</td>
<td>51 29 7 3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46 21 1 0</td>
<td>46 21 1 0</td>
<td>46 21 1 0</td>
<td>46 21 1 0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40 23 0 0</td>
<td>40 23 0 0</td>
<td>40 23 0 0</td>
<td>40 23 0 0</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36 34 1 0</td>
<td>36 34 1 0</td>
<td>36 34 1 0</td>
<td>36 34 1 0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35 17 1 0.4</td>
<td>35 17 1 0.4</td>
<td>35 17 1 0.4</td>
<td>35 17 1 0.4</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29 17 2 1</td>
<td>29 17 2 1</td>
<td>29 17 2 1</td>
<td>29 17 2 1</td>
</tr>
</tbody>
</table>

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=169)</th>
<th>Placebo (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81 70 21 0</td>
<td>81 70 21 0</td>
<td>81 70 21 0</td>
<td>81 70 21 0</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>70 36 6 0</td>
<td>70 36 6 0</td>
<td>70 36 6 0</td>
<td>70 36 6 0</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>69 35 1 0</td>
<td>69 35 1 0</td>
<td>69 35 1 0</td>
<td>69 35 1 0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>60 27 15 0</td>
<td>60 27 15 0</td>
<td>60 27 15 0</td>
<td>60 27 15 0</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>52 30 5 4</td>
<td>52 30 5 4</td>
<td>52 30 5 4</td>
<td>52 30 5 4</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43 17 1 0</td>
<td>43 17 1 0</td>
<td>43 17 1 0</td>
<td>43 17 1 0</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44 30 0 0</td>
<td>44 30 0 0</td>
<td>44 30 0 0</td>
<td>44 30 0 0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41 22 0 0</td>
<td>41 22 0 0</td>
<td>41 22 0 0</td>
<td>41 22 0 0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31 19 1 0</td>
<td>31 19 1 0</td>
<td>31 19 1 0</td>
<td>31 19 1 0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28 15 2 2</td>
<td>28 15 2 2</td>
<td>28 15 2 2</td>
<td>28 15 2 2</td>
</tr>
</tbody>
</table>

Table 5: Abnormal Laboratory Findings in ≥10% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Placebo (n=179)</th>
<th>Placebo (n=179)</th>
<th>Placebo (n=179)</th>
<th>Placebo (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>81 70 21 0</td>
<td>81 70 21 0</td>
<td>81 70 21 0</td>
<td>81 70 21 0</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>70 36 6 0</td>
<td>70 36 6 0</td>
<td>70 36 6 0</td>
<td>70 36 6 0</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>69 35 1 0</td>
<td>69 35 1 0</td>
<td>69 35 1 0</td>
<td>69 35 1 0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>60 27 15 0</td>
<td>60 27 15 0</td>
<td>60 27 15 0</td>
<td>60 27 15 0</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>52 30 5 4</td>
<td>52 30 5 4</td>
<td>52 30 5 4</td>
<td>52 30 5 4</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43 17 1 0</td>
<td>43 17 1 0</td>
<td>43 17 1 0</td>
<td>43 17 1 0</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>44 30 0 0</td>
<td>44 30 0 0</td>
<td>44 30 0 0</td>
<td>44 30 0 0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41 22 0 0</td>
<td>41 22 0 0</td>
<td>41 22 0 0</td>
<td>41 22 0 0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31 19 1 0</td>
<td>31 19 1 0</td>
<td>31 19 1 0</td>
<td>31 19 1 0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28 15 2 2</td>
<td>28 15 2 2</td>
<td>28 15 2 2</td>
<td>28 15 2 2</td>
</tr>
</tbody>
</table>

The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decrease, 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 who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.3 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest. Serious adverse reactions occurred in 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 (8%).
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

Anemia 51 27
Thrombocytopenia 52 28
Neutropenia 20 13

Gastrointestinal disorders

Nausea 67 10
Vomiting 44 8
Constipation 36 5
Abdominal pain 34 7
Diarrhea 17 0.2

General disorders and administration site conditions

Fatigue 56 7

Infections and infestions

Urinary tract infection 15 2

Investigations

Blood alkaline phosphatase increased 11 2
AST/ALT elevation 11 1

Metabolism and nutrition disorders

Decreased appetite 27 2
Musculoskeletal and connective tissue disorders

Musculoskeletal pain 29 3

Nervous system disorders

Headache 19 0.4
Dizziness 11 0

Psychiatric disorders

Insomnia 21 1

Renal and urinary disorders

Acute kidney injury 17 1

Respiratory, thoracic and mediastinal disorders

Dyspnea 22 3
Cough 13 0

Vascular disorders

Hypertension 14 5

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (n=463) %</th>
<th>Grades 3-4* (n=163) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Decreased gamma glutamyl transferase</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased sodi um</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

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

Anemia 51 27
Thrombocytopenia 52 28
Neutropenia 20 13

Gastrointestinal disorders

Nausea 67 10
Vomiting 44 8
Constipation 36 5
Abdominal pain 34 7
Diarrhea 17 0.2

General disorders and administration site conditions

Fatigue 56 7

Infections and infestions

Urinary tract infection 15 2

Investigations

Blood alkaline phosphatase increased 11 2
AST/ALT elevation 11 1

Metabolism and nutrition disorders

Decreased appetite 27 2
Musculoskeletal and connective tissue disorders

Musculoskeletal pain 29 3

Nervous system disorders

Headache 19 0.4
Dizziness 11 0

Psychiatric disorders

Insomnia 21 1

Renal and urinary disorders

Acute kidney injury 17 1

Respiratory, thoracic and mediastinal disorders

Dyspnea 22 3
Cough 13 0

Vascular disorders

Hypertension 14 5

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (n=463) %</th>
<th>Grades 3-4* (n=163) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Decreased gamma glutamyl transferase</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased sodi um</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>
GI Cancer Expert Sets His Sights on the Next Generation

by ANITA T. SHAFFER

Weijing Sun, MD, FACP, has solidified his role as an internationally renowned gastrointestinal (GI) oncology investigator having spent his career participating in research that has reshaped the treatment landscape for various histologies. Now he splits his attention between clinical research and another important area: mentoring the next generation of oncology leaders.

FEATURES

OncLive Peer Exchange®

Long-term Data for CDK4/6 Inhibitors Solidify Role in First-line HR+/HER2- Breast Cancer

By Brittany Lovely

OncPathways®

41  Tumor Agnostic Role of TMB Biomarker Faces Challenges

By Jane de Larigue, PhD

Clinical Trial in Focus

45  Osimertinib/Savolitinib Combo Looks to Overcome Acquired Resistance in EGFR-Mutant NSCLC

DEPARTMENTS

From the Editor

Unique Aspects of Maintenance Therapy in Oncology Require Careful Consideration

By Maurie Markman, MD

Medical World News®

10

FDA Digest

24

Drug Spotlight:

Dabrafenib (Tafinlar) and Tremetinib (Mekinist)
Your Link to *Everything* Oncology

OncLive® is proud to partner with the leading cancer care centers across the United States. We collaborate on educational content so oncology professionals will have the resources and information they need to improve patient outcomes.

Scan the QR code with your mobile device to discover the reach and visibility of our Strategic Alliance Partnership network.
Experts Lend Their Voices to the Next Generation

WITH CLINICAL DATA being released at conferences and in journals daily, absorbing updates across oncology can feel like trying to drink from a firehose. For young investigators, the field is shifting at a rapid pace and most oncologists are standing down the road of personalized medicine making their respective fields at once appear both wider and narrower as new subclassifications of disease enter the spotlight.

A few decades ago, in gastrointestinal (GI) cancers, the standard of care for various malignancies under the umbrella term was fluorouracil. Now, molecular classifications are guiding treatment decisions. For example, patients with chemotherapy-refractory HER2-positive metastatic colorectal cancer, a population with limited treatment options, have derived a clinical benefit with tucatinib (Tukysa) plus trastuzumab (Herceptin) according to data from the phase 2 MOUNTAINEER trial (NCT03043313).¹

Further, at the 2022 American Society of Clinical Oncology, data from a phase 2 study (NCT04165772) showed that patients with mismatch repair-deficient (dMMR) locally advanced rectal cancer (n = 14) elicited a 100% complete response rate with single-agent dostarlimab-gxly (Jemperli), a PD-1 inhibitor.²

These data, presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022 and 2022 American Society of Clinical Oncology Meeting, respectively, highlight only 2 avenues of dissemination. Contextualizing these data vs available and standard clinical practice options requires a trusted clinician in the space.

The collaborative spirit of Weijing Sun, MD, FACP, has earned the gastrointestinal oncology investigator the reputation of being a trusted voice in the field. In this issue’s cover story, Sun discusses the importance of taking the opportunity to partake in the guiding the next generation of leaders. “Our job is not just for ourselves but for the younger generation—to be their mentor, to encourage them, train them, and guide them,” Sun said. “You do have some authority, you do have a voice in pushing or guiding research funding, finding resources, or using your expertise and knowledge to guide and help afford training for the younger generation.”

One of the pillars of OncLive® is focused on providing our audience with access to leading investigators in the field to hear them discuss how pivotal data translate into practical application. Video programs, such as our OncLive Peer Exchange®, Insights, Rapid Readouts, and more, offer various formats for conveying the latest research in informational segments. Our editorial team is also dedicated to facilitating conversations among key opinion leaders on investigational efforts affecting the future of their specialties. In this issue’s Tumor Type Update, Edward Kim, MD, and Myron E. Schwartz, MD, discuss the benefits of radiation treatment options affecting the future of their specialties. In this issue’s Tumor Type Update, Edward Kim, MD, and Myron E. Schwartz, MD, discuss the benefits of radiation treatment options affecting the future of their specialties.

A LEADER IN CAR T-CELL IMMUNOTHERAPY

1st certified center in NJ to offer CAR T-cell therapy

AMONG THE NATION’S MOST EXPERIENCED BMT PROGRAM

Performed over 8,000 bone marrow transplants, averaging 400 a year

MORE CLINICAL TRIALS THAN ANY OTHER CANCER CENTER IN THE STATE

Enrolls over 1,500 patients each year in pivotal research studies

Hackensack Meridian John Theurer Cancer Center, one of the nation’s premier cancer programs.

Call 833-CANCER-MD to refer a patient.
Unique Aspects of Maintenance Therapy in Oncology Require Careful Consideration

by MAURIE MARKMAN, MD

HE TERM “MAINTENANCE THERAPY” has been applied to disease treatment in an increasing number of tumor types and clinical settings. But what is maintenance therapy and how does it differ from other strategies in cancer care? Maintenance therapy aims to maintain a response attained with the preceding antineoplastic drug regimen. Despite observed clinical benefits—for instance, elimination or substantial reduction of cancer-related symptoms or objective regression of measurable tumor masses—continuing certain regimens may not be feasible because of associated toxicities.

An example is administering carboplatin or cisplatin in treating advanced-stage ovarian cancer. Despite the major activity of the platinum drugs in this malignancy (with some therapies having an objective response rate above 80%), continuing treatment beyond 6 to 8 cycles likely will result in severe adverse effects (AEs) including peripheral neuropathy, renal dysfunction, and worsening emesis. Therefore, the goal of maintenance therapy would be maintaining the maximum clinical benefit achieved from the preceding cytotoxic strategy.

It is important to distinguish maintenance therapy from treatments that follow completion of an effective cytotoxic antineoplastic regimen. For example, clinicians may consider consolidation therapy for patients with hematologic malignancies who are highly responsive to chemotherapy. This approach is designed to intensify a treatment (eg, stem cell transplantation following a response to induction chemotherapy in acute myelocytic leukemia) with the goal of curing the malignancy. In this setting, 1 or possibly 2 cycles of an aggressive antineoplastic treatment will be administered, hopefully achieving this aim—a far different approach from the concept of maintenance.

Given the fundamental goals of maintenance therapy, there are additional issues to consider. First, an effective maintenance therapy regimen will be associated with a toxicity profile deemed acceptable over an extended period. This could be years rather than months in certain clinical settings, assuming the absence of disease progression.

Second, the extended delivery strategy inherent in a maintenance approach should be accomplished while minimizing time and effort required of patients. Weekly clinic visits or intermittent hospitalizations during initial cytotoxic treatment for a life-threatening malignancy may be appropriate. However, this would not be a rational approach for a maintenance strategy of 2 or 3 years. Monthly drug infusions or, preferably, oral regimens would be more in line with achieving goals of a maintenance approach to cancer treatment.

The toxicity profile of such extended treatment programs must be carefully considered. AEs considered acceptable for a highly effective induction regimen may be unacceptable in the maintenance setting. For example, patients with BRCa-mutant ovarian cancer may tolerate occasional intense emesis associated with platinum agents administered every 3 to 4 weeks for a maximum of 5 to 6 treatment courses. However, it is unlikely that even minimal nausea lasting several hours with each daily or twice-daily oral treatment with a PARP inhibitor would be acceptable for 2 to 3 years, despite the demonstrated efficacy of this maintenance strategy.

For decades, anticancer drug trials have focused on acute short-term AEs during a limited number of treatment cycles. Therefore, one must question whether these toxicity profiles objectively capture the negative effect on quality of life when delivered for several years in the maintenance setting.

The effects of longer-term and more chronic AEs associated with a maintenance strategy were highlighted in a study (NCT00003120) comparing 2 monthly paclitaxel regimens in women with ovarian cancer who had achieved a clinically defined complete response to platinum-based cytotoxic chemotherapy. With delivery of a 3-hour drug infusion once every 28 days minimizing the time patients spent in clinic or a physician’s office for therapy, investigators compared 3 monthly cycles of single-agent paclitaxel vs 12 monthly cycles. The longer regimen significantly improved the time to subsequent disease progression; however, the extended maintenance approach was associated with considerable risk for developing clinically significant grade 2/3 peripheral neuropathy. This was unlikely to be acceptable for patients and oncologists.

Finally, one must consider specific therapeutic goals justifying this cancer treatment approach beyond simply hoping to maintain a response, either objective (eg, decrease in size of tumor
masses, reduction in ascites, decrease in biomarkers of cancer) or subjective (eg, reduction in cancer symptoms). Permitting a patient to maintain an acceptable quality of life (as defined by the individual) for more prolonged periods than would be possible without a maintenance regimen is a legitimate goal of treatment. A critical point is that the patient defines what acceptable quality of life is, and not investigators on a peer-reviewed publication. Issues to be considered are the resulting AEs including low-grade events vs discontinuation of all antineoplastic therapy and observing the subsequent clinical course; time and effort required of the patient (and potentially family members) to receive therapy; and cost of the management program.

A statistically defined ($P < .05$) improvement in time to disease progression may be observed in a clinical trial of a maintenance strategy compared with an observation or placebo control. However, if the prolonged treatment period is associated with potentially distressing symptoms (eg, daily emesis), overall decreased quality of life (as defined by the patient), or if duration of benefit is modest (median of several months), one must critically ask what this approach has accomplished for most patients (and their oncologists).

A further consideration is understanding the effect of reintroducing alternative active antineoplastic regimens when there is documented progression but without the maintenance approach. If such therapy can rapidly reduce or eliminate recurrent signs and symptoms of disease with acceptable toxicity, it might challenge the benefits of a maintenance approach. This would be supported further if benefits of a maintenance strategy were anticipated to be limited in duration.

Conversely, such an outcome would be considered a therapeutic success if patients could resume many daily activities experienced prior to cancer diagnosis, AEs are manageable, and duration of outcomes is based on clinical trial data measured in many months or considerably longer. This has been documented, for example, in patients with ovarian cancer with a $BRCA$ mutation or homologous recombination repair defects treated with oral PARP inhibitors.$^{1,3}$

Nothing inherent in the concept of maintenance therapy suggests overall survival (OS) cannot or will not be improved by employing the approach. However, such an outcome should not be mandated in a phase 3 randomized trial evaluating and defining the clinical benefit of maintenance therapy. Delivery of 1 or more possible active treatments to patients in the experimental maintenance and control study arms following completion of trial-based therapy may make it difficult, if not impossible, to document a statistically significant effect on OS associated with the investigative regimen.

Finally, outcomes of maintenance therapy will vary greatly based on tumor type, status of disease, and available therapeutics—even with documenting what appears to be the same molecular defect (eg, $BRCA$ mutation) and employing the identical therapeutic (eg, PARP inhibitor) in different tumor types. This phenomenon is demonstrated by the striking improvement in progression-free survival associated with delivery of one of several PARP inhibitors in $BRCA$-mutated ovarian cancer vs administering the same class of drugs as maintenance in $BRCA$-mutated pancreatic cancer.$^{1,3}$ However, it is reasonable to anticipate that future research efforts will discover alternative molecular markers that can be therapeutically targeted by delivering the novel agents as a maintenance strategy in cancer management.

REFERENCES

Medical World News® is a first-of-its-kind online program for health care professionals, by health care professionals. The site provides video editorial content on a variety of cutting-edge topics delivered through a livestream and on demand for all health care stakeholders, offering the latest news and information in an easily digestible, one-stop-shop format.

INSIDE THE PRACTICE®
New Symptom Management App Puts Power in the Hands of Patients and Caregivers

University of Pittsburgh School of Nursing professor Heidi Donovan, PhD, RN, collaborated with PhD student Haomin (Leon) Hu to develop an app that focuses on patients and caregivers. The interactive symptom management app was designed to assist in the collection of patient-reported outcomes and self-management of adverse effects of treatment. The mobile health resource has the option to connect patients with health care providers or be used as a stand-alone resource. Additional features include a resource library, self-assessment tools, and goal-setting process.

TO WATCH, VISIT bit.ly/3b9X85d.

MEDICAL WORLD NEWS DEEP DIVE™
Diagnostic Breast Imaging During COVID-19

Breast radiologists are facing significant challenges in the aftermath of the COVID-19 pandemic, according to Amy K. Patel, MD, medical director of the Breast Care Center at Liberty Hospital in Missouri. In addition to workload issues, they may be seeing more patients presenting with advanced breast cancer due to pandemic-related screening delays. However, Patel noted there are also emerging opportunities to save lives, including offering resources to the community to educate individuals and provide more access for routine screenings.

TO WATCH, VISIT bit.ly/3Jhe1o5.

AFTER HOURS™
Music as Medicine When Treating Patients

Oncologist Steven G. Eisenberg, DO, finds that connecting with his patients at the California Care Associates for Research and Excellence is made stronger with the addition of song. In addition to using music to process events that happened and to destress, Eisenberg enjoys the doctor-patient relationships that music helps foster. Eisenberg takes a collaborative approach to the songwriting process, writing original music with his patients. “In the end, I think it’s really all about connection,” he said. “Laughter and music connect [individuals] very quickly.”

TO WATCH, VISIT bit.ly/3SlQ3wm.
KISQALI has accomplished what no other CDK4/6 inhibitor has—the longest median overall survival ever reported in HR+/HER2- mBC.

MONALEESA-2, a dedicated 1L postmenopausal trial: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI® (ribociclib) + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); P=0.004. In the primary analysis at a median follow-up of 15 months, mPFS was not reached (95% CI: 19.3-NR) vs 14.7 months (95% CI: 13.0-16.5); HR=0.556 (95% CI: 0.429-0.720); P<0.0001.2-4

Indications
KISQALI® (ribociclib) is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

IMPORTANT SAFETY INFORMATION

Interstitial lung disease/pneumonitis. Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors. Across clinical trials in patients with advanced or metastatic breast cancer treated with KISQALI in combination with an aromatase inhibitor or fulvestrant (“KISQALI treatment groups”), 1.1% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.3% had grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.
KISQALI is the only CDK4/6 inhibitor with statistically significant overall survival data reported in postmenopausal patients with an AI

See Dr Gabriel Hortobagyi share his perspectives on the data. “What this particular clinical trial has achieved… is an enormous step forward.” —Gabriel Hortobagyi, MD

IMPORTANT SAFETY INFORMATION (continued)

Interstitial lung disease/pneumonitis (continued). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis.

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients treated with KISQALI in the postmarketing setting.

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.
The longest median overall survival ever reported in HR+/HER2- mBC

MONALEESA-2: KISQALI + AI in 1L postmenopausal patients
At a median follow-up of 80 months

OVERALL SURVIVAL | KISQALI + Al

No. of events
KISQALI arm: 181, Placebo arm: 219
HR=0.765 (95% CI: 0.628-0.932); P=0.004

No. at risk
KISQALI + Al
334 323 315 305 300 284 270 253 237 220 202 191 180 165 158 150 142 135 125 101 48 8 0
Placebo + Al
334 326 316 306 293 283 265 244 222 209 195 183 167 149 139 131 114 104 94 73 38 6 0

Hazard ratios are based on stratified Cox model.

OVERALL SURVIVAL BENEFIT WITH KISQALI INCREASED OVER TIME
At 6 years, the survival rate of patients receiving KISQALI® (ribociclib) + letrozole was 44% vs 32% with placebo + letrozole.

PFS: In the primary analysis at a median follow-up of 15 months, mPFS was not reached with KISQALI + letrozole (95% CI: 19.3-NR) vs 14.7 months with placebo + letrozole (95% CI: 13.0-16.5); HR=0.556 (95% CI: 0.429-0.720); P<0.0001. In an updated analysis with a median follow-up of 26 months, mPFS was 25.3 months (95% CI: 23.0-30.3) vs 16.0 months (95% CI: 13.4-18.2).3-5

Study design: MONALEESA-2 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + letrozole (n=334) vs placebo + letrozole (n=334) in postmenopausal patients with HR+/HER2- mBC who received no prior therapy for advanced disease. OS was a secondary end point; PFS was the primary end point.3,4

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.
Important Safety Information (continued)

**Severe cutaneous adverse reactions (continued).** If SCARs is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

**QT interval prolongation.** KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 14 of 1054 patients (1%) had >500 ms postbaseline QTcF value, and 59 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

**Increased QT prolongation with concomitant use of tamoxifen.** KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the NSAI + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

**Hepatobiliary toxicity.** Across clinical trials in patients with advanced or metastatic breast cancer, increases in transaminases were observed. Across all trials, grade 3 or 4 increases in alanine aminotransferase (ALT) (10% vs 2%) and aspartate aminotransferase (AST) (7% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 85 days and median time to resolution to grade ≤2 was 22 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.
Neutropenia. Across trials, neutropenia was the most frequently reported adverse reaction (AR) (74%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 16 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 0.8%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryofetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryofetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. Across clinical trials of patients with advanced or metastatic breast cancer, the most common ARs reported in the KISQALI treatment groups (pooled incidence ≥20%) were neutropenia (74% vs 5%), nausea (45% vs 27%), infections (41% vs 30%), fatigue (33% vs 30%), diarrhea (30% vs 22%), leukopenia (30% vs 3%), vomiting (27% vs 16%), alopecia (24% vs 12%), headache (24% vs 22%), constipation (24% vs 16%), rash (21% vs 9%), and cough (21% vs 16%). The most common grade 3/4 ARs (reported at a pooled frequency >5%) were neutropenia (59% vs 1%), leukopenia (16% vs 3%), abnormal LFTs (9% vs 2%), and lymphopenia (5% vs 1%).

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm vs placebo arm (all grades, pooled incidence ≥20% and ≥5% higher than placebo arm) were leukocyte count decrease (94% vs 30%), neutrophil count decrease (93% vs 25%), hemoglobin decrease (66% vs 38%), lymphocyte count decrease (61% vs 26%), AST increase (47% vs 38%), ALT increase (44% vs 36%), creatinine increase (38% vs 13%), and platelet count decrease (31% vs 9%). The most common grade 3/4 laboratory abnormalities (incidence >5%) were neutrophil count decrease (59% vs 2%), leukocyte count decrease (32% vs 1%), lymphocyte count decrease (15% vs 4%), ALT increase (10% vs 2%), and AST increase (7% vs 2%).

1L=first line; AI=aromatase inhibitor; CDK=cell cycle-dependent kinase; ET=endocrine therapy; HR=hazard ratio; mBC=metastatic breast cancer; mOS=median overall survival; mPFS=median progression-free survival; NR=not reached; OS=overall survival; PFS=progression-free survival.

KISQALI® (ribociclib) tablets, for oral use


**BRIEF SUMMARY:** Please see package insert for full prescribing information.

### 1 INDICATIONS AND USAGE

**KISQALI** is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Intestinal Lymph Disease/Pneumonitis

Severe, life-threatening, or fatal intestinal lymph disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

- Across clinical trials (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.1% of KISQALI-treated patients had Grade 3 or 4 ILD/pneumonitis of any type, 0.3% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported [see Adverse Reactions (6.2)].

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis [see Dosage and Administration (2.2) in the full prescribing information].

#### 5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DISH)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI [see Adverse Reactions (6.3)].

If signs or symptoms of severe cutaneous reactions occur, interrupt KISQALI until the etiology of the reaction has been determined [see Dosage and Administration (2.3) in the full prescribing information]. Consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DISH/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life threatening cutaneous reactions during KISQALI treatment.

#### 5.3 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner [see Clinical Pharmacology (12.1) in the full prescribing information]. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 [see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.4)].

- Across MONALEESA-2, MONALEESA-7, and MONALEESA-3 in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (1%) had a > 500 ms post-baseline QTcF value, and 59 out of 1054 patients (6%) had a > 50 ms increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, on the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 [see Adverse Reactions (6.3)].

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy [see Dosage and Administration (2.2) in the full prescribing information].

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradycardia
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTc interval.

#### 5.4 Increased QT Prolongation With Concomitant Use of Tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF interval at baseline was > 10 ms higher in the tamoxifen plus placebo subgroup compared with the non-steroidal aromatase inhibitors (NSAIs) plus placebo subgroup. In the placebo arm, an increase of > 60 ms from baseline occurred in 6/80 (7%) of patients receiving tamoxifen, and in no patients receiving NSAIs. An increase of > 60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI [see Clinical Pharmacology (12.2) in the full prescribing information].

#### 5.5 Hepatobiliary Toxicity

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, 8% of patients (Grades 3 or 4) increased alanine aminotransferase (ALT) (10% vs. 2%) and aspartate aminotransferase (AST) (7% vs. 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥3 ALT/AST elevation, the median time-to-onset was 85 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≤2 was 22 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than twice the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated [see Dosage and Administration (2.2) in the full prescribing information].

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobiliary Toxicity) [see Dosage and Administration (2.2) in the full prescribing information]. Recommendations for patients who have elevated AST/ALT Grade ≥3 at baseline have not been established.

#### 5.6 Neutropenia

In MONALEESA-2, MONALEESA-7, and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (74%), and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 3, or 4 neutropenia, the median time to Grade 2 neutropenia was 16 days. The median time to resolution of Grade ≥3 (to normalization or Grade <3) was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Neutropenia was reported in 1% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 0.8%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6 [see Dosage and Administration (2.2) in the full prescribing information].

#### 5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose [see Use in Specific Population (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information].

### 6 ADVERSE REACTIONS

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

- Intestinal Lymph Disease/Pneumonitis
- Severe Cutaneous Adverse Reactions
- QT Interval Prolongation
- Hepatobiliary Toxicity
- Neutropenia

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

**MONALEESA-2: KISQALI in Combination with Letrozole**

Most common adverse reactions reported in patients in MONALEESA-2 are listed in Table 8 and Table 9, respectively.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo + Letrozole</th>
<th>KISQALI + Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>N = 247</td>
<td>N = 334</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 (4%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>75 (30%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>33 (13%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>18 (7%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11 (4%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>1 (&lt;1%)</td>
<td>6 (&lt;2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19 (7%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>1 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (9%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 (5%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 8: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-2 (All Grades)
KISQALI® (ribociclib) tablets, for oral use

CONTRAINDICATIONS

- Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may increase the risk of torsades de pointes.
- Risks of QT interval prolongation and torsades de pointes increase with increasing serum concentrations of KISQALI and with concomitant use of other P-glycoprotein substrates or strong CYP3A inhibitors.
- Hematologic disorders can lead to neutropenia, anemia, and lymphopenia. Neutropenia is the most common adverse reaction of KISQALI.

Laboratory Abnormalities

- Hematology: leukopenia, anemia, and lymphopenia, with most common ARs reported at a frequency ≥ 10% and ≥ 2% higher than placebo arm in MONALEESA-2 (Table 8).
- Chemistry: elevated levels of transaminases, increased levels of total bilirubin and alkaline phosphatase, decreased serum levels of sodium, potassium, and hemoglobin, and decreased white blood cell count (Table 9).

Interstitial Lung Disease/Pneumonitis

- Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI due to ILD or pneumonitis. Discontinue KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI if bronchospasm, cough, fever, hypoxia, increased respiratory rate, and/or bilateral pulmonary infiltrates develop.

Additional adverse reactions in MONALEESA-3 for patients receiving KISQALI plus letrozole included interstitial lung disease (0.5%), lung infiltration (0.3%), pneumonitis (0.3%), and pulmonary fibrosis (0.8%).

Additional adverse reactions in MONALEESA-7 for patients receiving KISQALI plus NSAI included asthenia (12%), thrombocytopenia (9%), dry skin (8%), oropharyngeal pain (7%), dyspepsia (5%), anemia (5%), hypertension (4%), allergic reaction (4%), and rash (4%).

Adverse Drug Reactions

Table 8: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-2 (All Grades)

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>KISQALI + letrozole N = 334</th>
<th>Placebo + letrozole N = 330</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>25</td>
<td>10</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>33</td>
<td>10</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>6</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>14</td>
<td>5</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>12</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>4</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>12</td>
<td>4</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>18</td>
<td>5</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional adverse reactions in MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant, included asthenia (14%), dry skin (8%), oropharyngeal pain (7%), dyspepsia (5%), anemia (5%), hypertension (4%), allergic reaction (4%), and rash (4%).

Table 9: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-2

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + letrozole N = 334</th>
<th>Placebo + letrozole N = 330</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Leukocyte count decreased</td>
<td>93</td>
<td>31</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>93</td>
<td>49</td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>57</td>
<td>2</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>51</td>
<td>12</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>29</td>
<td>1</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>KISQALI + NSAI + goserelin N = 248</th>
<th>Placebo + NSAI + goserelin N = 247</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>25</td>
<td>10</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>4</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>4</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 11: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-7

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + NSAI + goserelin N = 248</th>
<th>Placebo + NSAI + goserelin N = 247</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Leukocyte count decreased</td>
<td>93</td>
<td>34</td>
<td>34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>92</td>
<td>54</td>
<td>54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>84</td>
<td>2</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>55</td>
<td>12</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>28</td>
<td>1</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>21</td>
<td>2</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorous decreased</td>
<td>14</td>
<td>2</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>11</td>
<td>1</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, infections, and abnormal liver function tests. See Table 12.

Table 12: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-3 (All Grades)

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>KISQALI + fulvestrant N = 483</th>
<th>Placebo + fulvestrant N = 241</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infecions1</td>
<td>42 50</td>
<td>0 0</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>69 72</td>
<td>0 0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 12</td>
<td>0 0</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 3</td>
<td>0 0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16 13</td>
<td>0 0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>22 15</td>
<td>0 0</td>
</tr>
<tr>
<td>Cough</td>
<td>15 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 1</td>
<td>12 2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>45 28</td>
<td>0 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 1</td>
<td>20 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 0</td>
<td>13 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>25 1</td>
<td>12 0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17 1</td>
<td>13 0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>19 0</td>
<td>5 0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20 0</td>
<td>7 0</td>
</tr>
<tr>
<td>Rash</td>
<td>23 7</td>
<td>1 1</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15 0</td>
<td>7 0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Investigations</td>
<td>15 2</td>
<td>5 1</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13 5</td>
<td>1 1</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>13 5</td>
<td>1 1</td>
</tr>
</tbody>
</table>

Table 13: Laboratory Abnormalities Occurring in ≥ 10% of Patients in MONALEESA-3

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>KISQALI + fulvestrant N = 483</th>
<th>Placebo + fulvestrant N = 241</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count decreased</td>
<td>95 25</td>
<td>25 1</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>92 46</td>
<td>7 0</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>60 4</td>
<td>0 0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>69 14</td>
<td>1 3</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>33 1</td>
<td>1 1</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>65 6</td>
<td>1 1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>52 6</td>
<td>1 3</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>49 5</td>
<td>2 0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>44 8</td>
<td>3 2</td>
</tr>
<tr>
<td>Glucose serum decreased</td>
<td>23 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Phosphorous decreased</td>
<td>18 5</td>
<td>0 0</td>
</tr>
</tbody>
</table>

Summary of Clinical Studies:
- The median duration of exposure to KISQALI was 20.8 months (range: 0.5 to 36.0 months).

Other adverse reactions occurring in men treated with KISQALI plus letrozole and goserelin or leuproline were similar to those occurring in women treated with KISQALI plus endocrine therapy.

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of KISQALI. Because these events 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.

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations CYTP3A Inducers

Co-administration of a strong CYP3A4 inducer (rifampin) increased ribociclib exposure in healthy subjects by 3.2-fold [see Clinical Pharmacology (12.3) in the full prescribing information]. Avoid co-administration of strong CYP3A4 inhibitors (e.g., bepridil, pimozide, and ondansetron) with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

7.3 Effect of KISQALI on Other Drugs CYTP3A Substrates with Narrow Therapeutic Index

Co-administration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone [see Clinical Pharmacology (12.3) in the full prescribing information]. KISQALI given at the clinically relevant dose of 600 mg was predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYTP3A3 substrates with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of post implantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis. In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day. In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development, including increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lobe, extra/ rudimentary 13th ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollux. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from
KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data
In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential
Based on animal studies and mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to starting treatment with KISQALI.

Contraception
Females
Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility
Males
Based on animal studies, KISQALI may impair fertility in males of reproductive potential [see Non-clinical Toxicology (13.1) in the full prescribing information].

8.4 Pediatric Use
The safety and efficacy of KISQALI in pediatric patients has not been established.

8.5 Geriatric Use
Of 334 patients who received KISQALI in MONALEESA-2, 150 patients (45%) were ≥ 65 years of age and 35 patients (11%) were ≥ 75 years of age. Of 484 patients who received KISQALI in MONALEESA-3, 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) [see Dosage and Administration (2.2) in the full prescribing information]. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for Cmax, 1.28 for AUCtrue) and severe (GMR: 1.92 for Cmax, 1.29 for AUCtrue) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

8.7 Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73 m² ≤ estimated glomerular filtration rate [eGFR] < 90 mL/min/1.73 m²) or moderate (30 mL/min/1.73 m² ≤ eGFR < 60 mL/min/1.73 m²) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m²), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information].

10 OVERDOSAGE
There is limited experience with reported cases of overdose with KISQALI in humans. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
© Novartis
T2022-03
Acalabrutinib Tablet Formulation Is Approved for Current Indications

The FDA has approved a new tablet formulation of acalabrutinib (Calquence) for all current indications, including adult patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and for those with relapsed or refractory mantle cell lymphoma (MCL).

The regulatory decision was supported by data from the ELEVATE PLUS trials, in which the capsule and tablet formulations of the drug were determined to be bioequivalent, indicative that the same safety and efficacy can be expected from either formulation when using the same dose and schedule.

The three phase 1, open-label, single-dose, crossover studies were conducted in healthy patients to determine the pharmacokinetic (PK) similarity of the acalabrutinib tablet given at 100 mg vs the capsules given at 100 mg (n = 66).

Notably, the tablet formulation can be taken with gastric acid-reducing agents, including proton pump inhibitors, antacids, and H2-receptor antagonists. Most reported toxicities were mild and no new safety signals were observed with the tablet vs the capsule.

To Read More, Visit bit.ly/3AaR6Ir.

N-803 Is Under Consideration for BCG-Unresponsive NIMBC

The biologics license application for the IL-15 superagonist N-803 has been accepted for review by the FDA with an anticipated decision date of May 23, 2023. The agency will review data from the ongoing phase 2/3 QUILT-3.032 trial (NCT03022825) to support the agent’s use for the treatment of patients with bacillus Calmette-Guérin (BCG)–unresponsive non–muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS) with or without Ta or T1 disease. Cohort A of QUILT-3.032 included patients with CIS and cohort B included those with papillary histology. The median duration of response was 26.6 months among all treated patients (n = 154) and the overall response rate was 71%. All patients had a 12-month complete response (CR) rate of 62% (95% CI, 48%-74%) and a 52% CR rate at 24 months (95% CI, 37%-65%). The cystectomy avoidance rate was 93% and the 24-month rate of bladder cancer–specific progression-free survival was 91% (95% CI, 81.2%-95.4%). The overall survival rate was 100%.

To Read More, Visit bit.ly/3JqNVzp.

FDA Schedules Series of ODAC Meetings to Review Pending Drug Applications

The FDA has scheduled 3 sessions for the Oncologic Drugs Advisory Committee (ODAC) to review updates on the new drug application (NDA) for poziotinib tablets and data for the continued approval of indications for melphalan flufenamide (Pepaxto) and duvelisib (Copiktra). Final decisions on these agents will ultimately be made by the FDA.

First, on September 22, 2022, the committee will review data from the phase 2 ZENITH20 trial (NCT03318939) supporting the NDA for approval of poziotinib for patients with previously treated locally advanced or metastatic non–small cell lung cancer with HER2 exon 20 insertion mutations. The anticipated approval date is November 24, 2022. Among 90 patients, the objective response rate was 27.8% (95% CI, 18.9%-38.2%), with 25 patients having a partial response. The median duration of response was 5.1 months and the disease-control rate was 70%. Safety is a cited concern with the agent, with 87% of patients reporting dose interruptions.

During the second session, also scheduled for September 22, ODAC will discuss the benefit-risk ratio and continued approval of melphalan flufenamide for patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy and whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 CD38-directed monoclonal antibody. The agent received accelerated approval in 2021; however, data from the phase 3 OCEAN trial (NCT03151811) did not meet the primary end point of improved overall survival vs pomalidomide.

Lastly, on September 23, ODAC will review long-term data from the phase 3 DUO trial (NCT02004522), submitted as part of the postmarketing requirement for the continued approval of duvelisib for patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least 2 prior therapies. The FDA had approved the agent in 2018 based on earlier data from DUO. In June 2022 the agency issued a drug safety communication warning of an increased incidence of adverse effects, including infections, diarrhea, inflammation of the intestines and lungs, skin reactions, and high liver enzyme levels in the blood.

To Read More, Visit bit.ly/3OOg6Ju.
The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

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

To nominate, please visit: giantsofcancercare.com/nominate

PROGRAM OVERVIEW

- Nominations are open through January 31, 2023.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection committee of more than 120 oncologists will vote to determine the 2023 inductees.
- The 2023 Giants of Cancer Care® class will be announced in spring 2023.

Abbreviated Rules: NO PURCHASE NECESSARY. Contest begins on or about June 2, 2022 and ends on Tuesday, January 31, 2023 at 11:59 p.m. ET ("Contest Period"), with the option to extend the nomination period through February 28, 2023. Open only those who are 18 years of age or older at the time of entry and who are a licensed healthcare professional (i.e., MD, DO, PhD, and/or RN) working in the oncology space at the time of application and award. Subject to Official Rules. See Official Rules at www.giantsofcancercare.com for additional eligibility restrictions, prize descriptions, restrictions, and complete details. Odds of winning depend on the number of eligible entries received. Void where prohibited. Sponsor: Intellisphere, LLC.
Drug Spotlight

DABRAFENIB (TAFINLAR) and TRAMETINIB (MEKINIST)

Tumor Agnostic Approval Targets BRAF V600E–Mutant Disease

by MEGAN HOLLASCH

The FDA has granted accelerated approval to the combination of dabrafenib (Tafinlar) and trametinib (Mekinist) for adult and pediatric patients 6 years or older with unresectable or metastatic Braf V600E–mutant solid tumors. Patients must have been disease progression following prior treatment and have no satisfactory treatment options. The safety and efficacy of the combination were evaluated in 131 adult patients from open-label, multiple cohort trials (NCT02034110) and NCI-MATCH (NCT02465060) and 36 pediatric patients from the CTM212X2101 trial (NCT02124772).

The studies included 24 tumor types. Individuals in ROAR had high-grade glioma (HGG), biliary tract cancer, low-grade glioma (LGG), adenocarcinoma of small intestine, gastrointestinal stromal tumor, and anaplastic thyroid cancer. NCI-MATCH Subprotocol H included patients with Braf V600E–positive solid tumors (excluding melanoma, thyroid cancer, and colorectal cancer [CRC]), and the pediatric trial included patients with refractory or recurrent LGG or HGG.

The objective response rate (ORR) was 41% among the 131 adult patients (95% CI, 33%-50%). Among the highest representative tumor types, ORR was 46% (95% CI, 31%-61%) for biliary tract cancer, 33% (95% CI, 20%-48%) for HGG (combined adult and pediatric) and 50% (95% CI, 23%-77%) for LGG (combined adult and pediatric). Among all pediatric patients, the ORR was 25% (95% CI, 12%-42%) with 78% of patients having a response lasting at least 6 months and 44% of responders having a response lasting at least 24 months.

"This is a known [combination] that’s already been approved [by the FDA] for 3 different indications, the [adverse] effects are known and managed by oncologists, and we know that Braf V600E are actionable across these 3 tumor types [melanoma, non–small cell lung cancer (NSCLC), anaplastic thyroid cancers]," Vivek Subbiah, MD, said. "This important tissue agnostic approval across solid tumors provides access to patients with rare malignancies."

In an interview with OncologyLive®, Subbiah, an associate professor and clinical medical director of the Clinical Center for Targeted Therapy in the Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston discussed the significance of the approval and future directions for tumor agnostic drug development.

What is the significance of the FDA approval of the combination in this population and how do you see it affecting current practice patterns?

The FDA granted accelerated approval to dabrafenib, which is a BRAF inhibitor, in combination with trametinib, which is a MEK inhibitor, for the treatment of adult and pediatric patients [age] 6 years [or older] with unresectable metastatic solid tumors that harbor the Braf V600E mutation who have followed and progressed following prior treatment and have no satisfactory alternative treatment. The BRAF and MEK inhibitor combination is approved for melanoma, NSCLC, and anaplastic thyroid cancer. The lack of clinical benefit in BRAF inhibition and Braf V600E–mutated CRC had prevented its tissue agnostic developing.

The MAP kinase pathway was first implicated in the pathogenesis of melanoma and since then, we have 3 different combinations that have shown activity and are FDA approved in melanoma specifically harboring BRAF V600E mutations. The main challenge is that BRAF V600E mutations [across] all malignancies. We reviewed case reports, outcomes of patients with BRAF–mutated nonmelanoma malignancies [and saw that] BRAF V600E mutations are prevalent across multiple nonmelanoma malignancies [with] more than 20 different tumor types harboring this mutation. They lead to oncogene addiction across all these tumor types and are clinically actionable in a broad variety and range of other and pediatric nonmelanoma malignancies. CRC remained an exception.

What are the implications on routine diagnostics?

I think the combination of dabrafenib and trametinib demonstrate meaningful efficacy in multiple BRAF-mutant tumor types, including some patients with rare cancers who have no alternative treatment options. Physicians should consider a BRAF test as a routine diagnostic test step that could enable this new treatment option for patients with many solid tumors. Specifically, we need comprehensive next-generation sequencing in patients with solid tumors so that patients can benefit from BRAF targeted therapy.

Based on this approval, and others in the past, do you believe that the field of oncology is headed toward more tumor agnostic approvals? Or will it be used as a tool for rarer subsets?

I think it's going to be a combination of both, think there will be more tissue agnostic approvals, especially for targets that share biomarkers across different tumor indications. We see these biomarkers in rare cancers more than common cancers. We are learning [about these] are new approvals, new targets, and new medications.

The first ever tissue agnostic agent that was approved was immunotherapy, pembrolizumab [Keytruda], for [patients with] mismatch repair deficient [dMMR] microsatellite instability-high tumors. The second drug was larotrectinib [Vitrakvi] for antifusion paths to solid tumors. The third drug was entrectinib [Rozlyrie], and subsequently pembrolizumab also received approval for [patients with high] tumor mutation burden. More recently, dostarlimab-gxly [Jemperli] was approved in a histology agnostic manner for patients with dMMR and there is a VHL-targeted agent also approved with a tissue agnostic indication.

The new kid on the block, Braf V600E, has been a specific target for the past decade, but for patients beyond melanoma, lung cancer, or anaplastic thyroid cancer, those harboring BRAF mutations did not have any approved therapy, especially patients with CRC, HGGs, or LGGs. This approval will provide access for these patients.

Is there anything else that you would like to add?

My personal belief is universal genomic testing is needed to move our needle against cancer. I think the more comprehensive tests we do in patients the earlier in the disease course, more patients will benefit from these therapies.

REFERENCE

FDA approval—June 22, 2022
FDA grants accelerated approval to dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for adult and pediatric patients 6 years and older with unresectable or metastatic solid tumors with a BRAF V600E mutation who have progressed following prior treatment and have no alternative treatment options.

Mechanism of action
- Dabrafenib and trametinib target 2 different kinases in the RAS/RAF/MEK/ERK pathway; use of the drugs in combination resulted in greater growth inhibition of BRAF V600 mutation–positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive tumor xenografts compared with either drug alone.

How supplied
- Dabrafenib: 50-mg, 70-mg capsules
- Trametinib: 0.5-mg, 2-mg tablets

Dose
- Dabrafenib: 150 mg orally twice daily; pediatric dosing is based on body weight
- Trametinib: 2 mg orally once daily; pediatric dosing is based on body weight

Company: Novartis

PIVOTAL CLINICAL TRIALS
ROAR (NCT02034110) was a multi-cohort, multi-center, nonrandomized, open-label trial which enrolled adult patients with BRAF V600E–mutant tumors. NCI-MATCH (NCT02465060), a single-arm, open-label study enrolled with adult patients with solid tumors cancers excluding melanoma, thyroid cancer, and colorectal cancer. CTMT212X2101 trial (NCT02124772) study was a pediatric multi-center, open-label, multiple cohort study in patients, median age of 10 years old, with refractory or recurrent solid tumors. Part C was a dose escalation of dabrafenib in combination with trametinib in patients and Part D was a cohort expansion phase of dabrafenib in combination with trametinib in patients with LGG.

Efficacy Results in ROAR and NCI-MATCH
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>ORR (95% CI)</th>
<th>DOR, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract cancer (n = 48)</td>
<td>46% (31%-61%)</td>
<td>1.8-40*</td>
</tr>
<tr>
<td>HGG (n = 48)</td>
<td>33% (20%-48%)</td>
<td>3.9-44*</td>
</tr>
<tr>
<td>LGG (n = 14)</td>
<td>50% (23%-77%)</td>
<td>7-23</td>
</tr>
<tr>
<td>Low-grade serous ovarian carcinoma (n = 5)</td>
<td>80% (28%-100%)</td>
<td>12-42</td>
</tr>
<tr>
<td>Adenocarcinoma small intestine (n = 4)</td>
<td>50% (7%-93%)</td>
<td>7-8</td>
</tr>
</tbody>
</table>

*Median DOR 9.8 months (95% CI, 5.3-20.4).

Efficacy Results in CTMT212X2101
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabrafenib plus trametinib (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>25% (12%-42%)</td>
</tr>
<tr>
<td>DOR ≥ 6 months</td>
<td>78%</td>
</tr>
<tr>
<td>DOR ≥ 24 months</td>
<td>44%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Dabrafenib plus trametinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>55% 4.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50% 5%</td>
</tr>
<tr>
<td>Rash</td>
<td>40% 2.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27% 1.5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26% 2.9%</td>
</tr>
<tr>
<td>Cough</td>
<td>29% 0%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>29% 4.4%</td>
</tr>
</tbody>
</table>

ADVERSE EFFECTS IN ADULT AND PEDIATRIC PATIENTS

EFICACY RESULTS IN CTMT212X2101

REFERENCES
WHEN WEIJING SUN, MD, FACP, started his career in oncology more than 30 years ago, the choice of medical treatment for patients with gastrointestinal (GI) malignancies was dominated by fluorouracil (5-FU), regardless of the tumor type.

"For treating all GI cancer, the only really effective drug was 5-FU," Sun recalled in a recent interview with OncologyLive®. "If you were treating colon cancer, it was 5-FU; stomach cancer, it was 5-FU. We tried to modify the regimen by prolonging infusion, with weekly infusion or daily infusion. We tried to maximize the benefit."

Instead of becoming discouraged by such limited options, Sun was motivated to explore potential new treatments with drug development. He became a prolific investigator into novel agents and combinations across a range of GI malignancies, serving as an institutional principal investigator in more than 40 clinical trials involving hepatocellular carcinoma (HCC) and colorectal, esophageal, gastric, and pancreatic cancers.

Today, Sun is an internationally known GI cancer expert. He is the Sprint Professor of Medical Oncology and director of the Medical Oncology Division at The University of Kansas School of Medicine and associate director of The University of Kansas Cancer Center (KU Cancer Center), a National Cancer Institute (NCI)-designated comprehensive cancer center, both headquartered in Kansas City.

Although he retains an interest in research, some of Sun’s focus has shifted to serving as a physician leader seeking to foster discussion about optimal treatment strategies among practicing oncologists and mentoring the next generation of providers. In that capacity, Sun is helping to shape the agenda for the upcoming 19th Annual Meeting of the International Society of Gastrointestinal Oncology® (ISGIO®), which is scheduled to take place September 30 through October 1, 2022, in Nashville, Tennessee. Sun serves as president of ISGIO® and is cochairing the meeting (SIDEBAR).

“Our job is not just for ourselves but for the younger generation—to be their mentor, to encourage them, train them, and guide them,” said Sun, noting that many GI physicians have been practicing 30 years or longer. “We’re obligated to transfer the baton to the next generation.”

“Physician leaders are important,” he noted. “You do have some authority, you do have a voice in pushing or guiding research funding, finding resources, or using your expertise and knowledge to guide and help afford training for the younger generation. That’s one of the reasons why I am involved and interested in doing some administrative jobs.”

“Of course, I’m still seeing patients in clinical trials,” he added. “Sometimes it seems like I have 3 jobs. Sometimes it’s overwhelming, sometimes it’s tiring. On the other hand, the reward is something you might not be able to see... You have a voice. If you’re not at the table, you don’t know what was discussed.”

Among his colleagues, Sun is known for his collaborative spirit. “He has been a lifelong contributor to GI cancer research and team science and has made a significant impact on that,” said John Marshall, MD, chief of the division of hematology/oncology at Medstar Georgetown University Hospital and director of the Otto J Ruesch Center for the Cure of Gastrointestinal Cancer, both in Washington, DC. “He is one of those people who represent what is good about the field. He gets the big picture and is engaged in making sure the next generation comes along but also is the kind of person who will share thoughts that are sometimes hard to share.”

In addition to his research activities, Sun has helped shaped the conversation in GI malignancies through his participation in cooperative group steering committees and task forces, conference program committees, and editorial boards of peer-reviewed journals, noted Tanios S. Bekaii-Saab, MD, a professor at Mayo Clinic College of Medicine and Science and
a consultant in the Division of Hematology/Oncology at Mayo Clinic in Scottsdale, Arizona. Bekaii-Saab serves as program chair for the upcoming ISGIO meeting. "He is definitely one of the most prominent figures in gastrointestinal cancers not just nationally, but internationally," Bekaii-Saab said. "He has really developed his career and expertise with a focus on drug development with biologic and targeted therapies and, more so these days, focused on immune-related research. . . He’s one of the prominent figures in GI oncology who have helped transform the field in many ways."

**ADVANCEMENTS IN GI LANDSCAPE**

Although Sun sees many unmet needs throughout the GI cancer field, particularly in pancreatic cancer, he said encouraging findings were presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting in 3 major areas: (1) results of a large-scale study that help guide the treatment of patients with metastatic colorectal cancer (mCRC); (2) evidence of complete responses (CRs) with single-agent immune checkpoint inhibitor therapy for a subset of patients with locally advanced rectal cancer; and (3) signs of clinical utility for circulating tumor DNA (ctDNA) analysis to help inform adjuvant therapy recommendations for colon cancer.1-3

*A New Standard Forms in mCRC*

In the phase 3 PARADIGM trial (NCT02394795), investigators sought to determine whether the addition of an EGFR inhibitor vs a VEGF inhibitor to chemotherapy would be a more effective regimen for patients with unresectable RAS wild-type mCRC. Previous studies in drugs with these mechanisms have yielded inconsistent results.1

In PARADIGM, patients were randomly assigned to receive either panitumumab (Vectibix), an EGFR inhibitor, or bevacizumab (Avastin), a VEGF inhibitor, plus modified FOLFOX-6 (oxaliplatin, leucovorin calcium, and 5-FU). The FDA has approved both agents for mCRC settings,1,3 but PARADIGM is the first trial to compare the drugs plus standard chemotherapy prospectively.1

Although patients with unresectable disease on either side of the colon were eligible to participate in the study, the primary end point was overall survival (OS) in participants with a left-sided primary tumor, defined as the descending colon, sigmoid colon, rectosigmoid, and rectum. If that benchmark proved statistically significant, defined as \( P < .04202 \), the OS in the overall population would be calculated, with a \( P < .05 \) threshold for significance.

Overall, 823 patients were recruited from May 2015 to June 2017. The efficacy-evaluable population comprised 400 patients in the panitumumab arm, including 312 with left-sided disease, and 402 patients in the bevacizumab arm, including 292 with left-sided tumors.

After a median follow-up of 61 months, the median OS among patients with left-sided tumors favored panitumumab at 37.9 months (95.8% CI, 34.1-42.6) compared with 34.3 months (95.8% CI, 30.9-40.3) with bevacizumab (HR, 0.82; 95.8% CI, 0.68-0.99; \( P = .031 \)). In the overall population, median OS was 36.2 months (95% CI, 32.0-39.0) with panitumumab vs 31.3 (95% CI, 29.3-34.1) with bevacizumab (HR, 0.84; 95% CI, 0.72-0.98; \( P = .030 \)). However, a subgroup analysis showed that panitumumab was not more beneficial than bevacizumab for patients with right-sided tumors (HR, 1.06; 95% CI, 0.77-1.45).1

The findings support panitumumab plus modified FOLFOX-6 as a first-line therapy for patients with RAS wild-type left-sided mCRC, investigators concluded. “That’s very important because it confirms the treatment standard for this population,” Sun said.

**Immunotherapy Stirs Excitement in Rectal Cancer**

In the rectal cancer field, initial results from a phase 2 study (NCT04165772) suggest that single-agent therapy with dostarlimab-gxly (Jemperli), a PD-1 inhibitor, may enable patients with mismatch repair-deficient (dMMR) locally advanced disease to avoid the debilitating effects of other therapeutic options.2

Single-agent therapy with dostarlimab, administered intravenously at 500 mg every 3 weeks for 6 months, resulted in a 100% CR rate in the first 14 patients, according to findings presented at 2022 ASCO and reported simultaneously in the 2022 ASCO and reported simultaneously in the

**ISGIO® Meeting Puts Accent on Expertise and Practical Insights**

by ANITA T. SHAFFER

**EXPERT PERSPECTIVES ON INTEGRATING**

the latest research data into clinical practice will mingle with findings from original abstracts during the upcoming 19th Annual Meeting of the International Society of Gastrointestinal Oncology® (ISGIO®).

This year’s meeting will feature presentations from investigators who have led key trials as well as opportunities for fellows to participate in the conference, according to Tanios S. Bekaii-Saab, MD, who serves as program chair. Bekaii-Saab is a professor of medicine at Mayo Clinic College of Medicine and Science and a consultant in the Division of Hematology/Oncology at Mayo Clinic in Scottsdale, Arizona.

The multidisciplinary meeting is scheduled to take place September 30 through October 1 in Nashville, Tennessee. Physicians’ Education Resource®, LLC (PER®) is hosting the conference as an interactive hybrid meeting with in-person presentations and online access.

The timing of the conference will enable the faculty to delve into research from the major conferences held throughout the year, including the American Society of Clinical Oncology Annual Meeting and the European Society for Medical Oncology Congress, Bekaii-Saab noted. This year’s faculty includes experts from throughout the United States, as well as speakers from Mexico and Brazil.

"The meeting is essentially the year in summary and how changes in gastrointestinal oncology will affect clinical practice, but it also sets the tone for what’s going to come in terms of transformative research," Bekaii-Saab said.

The conference will offer opportunities for practicing oncologists to go beyond the "raw data" from clinical studies, said Weijung Sun, MD, FACP, president of ISGIO® and cochair of the meeting. Sun is the Sprint Professor of Medical Oncology and director of the Medical Oncology Division at the University of Kansas School of Medicine and associate director of the University of Kansas Cancer Center (KU Cancer Center), both headquartered in Kansas City.

"We have all this clinical trial information, but how do you use the information day in and day out to treat the patient in front of you?" Sun said. "You want to know when to use it, which is appropriate patient, and how you distinguish [among clinical factors]."

The agenda includes Medical Crossfire® debates on sequencing treatment for resectable pancreatic cancer, first-line therapy for advanced hepatocellular carcinoma, the evolving standard of care for rectal cancer, and the use of liquid-only vs tissue-based biopsy.

There also will be more opportunities for fellows to participate this year through abstracts and presentations. "They’re going to be side by side with some of the leaders in the field across the world," Bekaii-Saab said.

For further information, visit bit.ly/38Ba80V.
GI Cancer

New England Journal of Medicine. A median follow-up of 6.8 months, none of the patients needed the standard treatment options of chemotherapy, radiation, or surgery. "This is very, very encouraging and almost a surprise," Sun said, adding that there was no evidence of tumor on endoscopic and MRI follow-up evaluations. "We probably need some larger study to verify the information, but this could change the way we're treating this small relatively specific patient population."

The first goal of treatment for patients with rectal cancer is curative therapy, Sun noted, but it also is important to preserve rectal function, if possible. The findings have implications not only for patients with dMMR rectal cancer, estimated at 5% to 10% of those diagnosed with the malignancy, but in other tumor types, according to investigators. The population of patients with tumor-agnostic, dMMR early-stage disease represents about 3% to 4% of all cancers, they said. In February 2022, the FDA granted an accelerated approval to dostarlimab for patients with dMMR recurrent or advanced solid tumors after prior therapy.

cT DNA Technology Moves Forward

The traditional TNM system for staging cancers by evaluating the primary tumor, regional lymph nodes, and distant metastasis has many limitations when used to assess whether patients with colon cancer would benefit from adjuvant therapy, Sun said. Some patients are treated unnecessarily, he explained, resulting in more toxicity from chemotherapy than benefit from treatment.

Against this backdrop, Sun said, developments in ctDNA technology offer the potential for noninvasive monitoring that helps guide treatment decisions, particularly for patients at high risk of recurrence. Study data have suggested that high levels of ctDNA in the blood correlate with a poor prognosis, Sun noted.

At ASCO 2022, findings from the DYNAMIC trial (ACTRN12615000381583) demonstrated that ctDNA levels correlated with recurrence-free survival (RFS) in patients with fully resected stage II colon cancer, with no evidence of metastatic disease on a CT scan within 8 weeks of surgery. Investigators randomly assigned participants 2:1 to ctDNA-guided treatment vs standard adjuvant therapy based on conventional clinical-pathologic criteria. The primary end point was the RFS rate at 2 years.

For the ctDNA arm, investigators conducted targeted sequencing on resected tumor tissue to identify mutations unique to each patient’s tumor from a panel of 15 genes recurrently altered in CRC. If at least 1 of these mutations was detected, ctDNA derived from plasma was analyzed at weeks 4 and 7 for the presence of the aberration. Participants with a positive ctDNA result at either testing point received adjuvant chemotherapy with an oxaliplatin-based doublet or single-agent fluoropyrimidine, whereas those with a negative result went on to observation.

The intent-to-treat population was comprised of 294 patients in the ctDNA-guided arm and 147 participants in the standard-therapy group. In the ctDNA group, 45 patients (15%) went on to receive adjuvant chemotherapy; all patients in the standard-management arm had chemotherapy.

After a median follow-up of 37 months, the 2-year RFS rate was 93.5% with ctDNA-guided therapy vs 92.4% with standard protocols. The 1.1% difference in the rate (95% CI, –4.1% to 6.2%) confirmed the noninferiority of the ctDNA-guided strategy, investigators said. The 3-year RFS rate was 92.5% for patients with negative ctDNA compared with 86.4% for those with positive levels. Investigators said the low recurrence rate among patients with negative ctDNA shows that they are unlikely to benefit from chemotherapy.

Although the DYNAMIC trial attracted attention at 2022 ASCO, many other studies into the clinical utility of ctDNA in GI cancers are ongoing, Sun noted.

IMPACT OF EARLY-PHASE RESEARCH

Over the years, Sun has published more than 125 peer-reviewed articles and presented approximately 100 abstracts and posters at conferences. At 2022 ASCO, he and colleagues presented early findings from a phase 2 study (NCT03488667) into the use of perioperative therapy with pembrolizumab (Keytruda) plus FOLFOX in patients with newly diagnosed locally advanced adenocarcinoma of the distal esophagus, gastroesophageal junction, and stomach.

Participants in the study receive neoadjuvant therapy with pembrolizumab at 200 mg every 3 weeks for 3 doses plus mFOLFOX every 2 weeks for 4 doses and then proceed to surgical resection if there is no evidence of metastatic disease. Following surgery, participants receive adjuvant therapy with mFOLFOX every 2 weeks for 4 doses plus pembrolizumab at 200 mg every 3 weeks for 12 doses. The primary end point is pathological response rate (ypR R) with a tumor regression score (TRS) of 2 or less.

Of 37 patients who finished preoperative treatment at the time of the 2022 ASCO presentation, 29 participants went on to receive curative-intent (R0) resections. Of those who had surgery, 26 patients (90%) demonstrated a pathological response (ypRR) with a TRS of 2 or less, including 6 patients (20%) who achieved a complete ypRR with a TRS of 0. Overall, 21 patients completed all phases of the treatment plan; 2 patients had recurrent or metastatic disease at 9 months and 10 months, respectively, and 1 patient died 23 months after enrollment. The other patients were cancer free at the time of the presentation.

The findings show that the combination can be safely administered, and the efficacy data are "very encouraging," Sun and colleagues said.

SUN, CONTINUED ON PAGE 30 ➤
Physicians’ Education Resource®, LLC (PER®), is pleased to present the 19th Annual Meeting of the International Society of Gastrointestinal Oncology®, a 2-day, multidisciplinary educational conference dedicated to presenting and discussing the latest advances in the broad field of gastrointestinal (GI) cancer research, as well as critical issues relevant to the care of people with GI cancer.

GI malignancies are often difficult to treat because of their heterogeneity, and the optimal management of these tumors often requires a high level of multidisciplinary cooperation and multimodality treatment regimens.

This highly engaging conference brings together world-renowned experts from different disciplines to educate you using a combination of case-based learning, debates, panel discussions, and didactic segments. Throughout the educational sessions, you will have numerous opportunities to interact with the presenting faculty.

Tanios Bekaii-Saab, MD, FACP
Professor of Medicine
Mayo Clinic College of Medicine and Science
Program Leader, Gastrointestinal Cancer
Consultant, Division of Hematology/Oncology
Mayo Clinic Cancer Center
Consortium Chair
Academic and Community Cancer Research United
Phoenix, AZ

Weijing Sun, MD, FACP
The Sprint Professor of Medical Oncology
Director, Division of Medical Oncology
University of Kansas School of Medicine
Associate Director for Clinical Research,
University of Kansas Cancer Center
Kansas City, KS

Accreditation/Credit Designation
Physicians’ Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This activity has been approved for 11.25 AMA PRA Category 1 Credits™.

Acknowledgement of Commercial Support
This activity is supported by educational grants from AstraZeneca, Daiichi Sankyo, Inc; Exelixis, Inc; Novartis Pharmaceuticals Corporation, and Taiho Oncology, Inc.

Scan QR code with a smartphone or visit the URL below
gotoper.com/ISGIO2022

35% off registration!
Register with code ISGIO35
Early-phase data such as those of the ASCO presentation might not produce immediate results but are helpful in setting the stage for future investigations, Sun said. When asked which research accomplishment he was most proud of, Sun pointed to studies he conducted in the mid-2000s into the combination of bevacizumab plus chemotherapy for treating patients with advanced or metastatic HCC. At the time, bevacizumab was approved for mCRC. Sun’s findings showed that the combination was a tolerable and effective option for this population.12,13

Although that regimen has not been approved for liver cancer, bevacizumab entered the HCC paradigm in June 2020 in combination with atezolizumab (Tecentriq), a PD-L1 inhibitor, for patients with unresectable or metastatic HCC who have not received prior systemic therapy.14

“These kinds of early data are very important,” Sun said. “Sometimes the reward may not necessarily be recognized immediately but the reason we do science is to try and advance the science to make the treatment option available. It’s not because want to be popular or to be famous.”

In that regard, Sun has extensively explored the role of angiogenesis, the process of blood vessel formulation that feeds tumor growth, in HCC and other GI malignancies. As a VEGF inhibitor, bevacizumab is perhaps the best-known anticancer therapy that targets angiogenesis.13,14

A FAR-FLUNG CAREER

In terms of his career, Sun’s journey had been as diverse as his research portfolio. After obtaining his medical degree from Shanghai Medical University (now Fudan University) in China in 1982, Sun practiced there for several years before immigrating to the United States in the late 1980s where he participated in postdoctoral and clinical fellowship programs. In 2001, Sun joined the faculty of the University of Pennsylvania School of Medicine in Philadelphia, Pennsylvania, as an assistant professor. He rose through the ranks to become director of GI medical oncology at the school of medicine and at the university’s Abramson Cancer Center from July 2008 through July 2012.

In September 2012, Sun joined the University of Pittsburgh School of Medicine, also in Pennsylvania, where he was director of the GI cancers section of hematology-oncology and co-director of the UPMC Gastrointestinal Cancer Prevention and Treatment Center.

Five years ago, Sun accepted his current multi-faceted roles at the University of Kansas. In doing so, he went from a state with 5 NCI–designated centers, including 3 cancer centers and a basic laboratory cancer center in Philadelphia alone, to a state where there is one. KU Cancer Center became the state’s only NCI-designated cancer center in 2012.15

In July 2022, KU Cancer Center was recognized as a comprehensive cancer center, a designation encompassing a greater depth and breadth of research that has been awarded to 53 centers nationwide. The honor caps a nearly 20-year effort to gain the NCI’s highest status, and KU Cancer Center leaders expect the designation will open the door to an increase in federal research funding.16

Sun said the center’s pursuit of comprehensive cancer center status was one of the reasons he accepted a position there. Many medical resources are concentrated on the East and West coasts, while patients in rural or otherwise underserved populations have unmet needs, he observed. “If I can contribute to making the cancer center a high-level [institution]—the university is one of the tops in the nation now—that will be a tremendous reward for me personally,” he said.17

REFERENCES

IS MYELOFIBROSIS TREATMENT ILL-FITTED TO PATIENT NEEDS?

Not all options are sufficient for all patients — which leaves them with less than optimal outcomes.¹ New approaches must be pursued to manage a fuller range of signs and symptoms in myelofibrosis.

TO LEARN MORE, VISIT MYELOFIBROSISINSIGHTS.COM

© 2022 Sierra Oncology, Inc. All Rights Reserved. May 2022 MRL 22-037
Long-term Data for CDK4/6 Inhibitors Solidify Role in First-line HR+/HER2- Breast Cancer

CDK4/6 INHIBITORS HAVE CARVED out a substantial role in the treatment of patients with hormone receptor-positive, HER2-negative breast cancer. The first approval of palbociclib (Ibrance) launched a series of trials examining the efficacy of agents in the frontline setting for these patients both as monotherapy and in combination with aromatase inhibitors (AIs).

“We have come a very long way in the treatment of hormone receptor-positive disease,” Komal Jhaveri, MD, said in a recent OncLive Peer Exchange® program. “What has really been a big paradigm shift and a big revolutionary treatment paradigm now is the addition of CDK4/6 inhibitors with an endocrine therapy.” Three CDK4/6 inhibitors are approved for patients with advanced hormone receptor-positive, HER2-negative metastatic breast cancer: abemaciclib (Verzenio), ribociclib (Kisqali), and palbociclib.1-3

During the panel discussion breast cancer experts contextualized how longer-term, retrospective, and real-world data presented during the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting and the European Society for Medical Oncology (ESMO) Breast Cancer Congress 2022 are continuing to drive clinical improvements for these patients. “It’s an exciting time to hear about the advances we’re making in this most common subset of breast cancer, the most common cancer worldwide in women,” moderator Hope S. Rugo, MD, FASCO, said.

CDK4/6 INHIBITORS HOLD STRONG IN FIRST LINE

The 2022 ASCO Annual Meeting featured updates from several key trials of CDK4/6 inhibitors for the treatment of patients with advanced hormone receptor-positive, HER2-negative metastatic breast cancer. Patient selection for this therapy accounts for several factors, but Anne P. O’Dea, MD, said that most of the patients she treats in this setting will receive a CDK4/6 inhibitor. “The overwhelming totality of data that was [available] really supports the use of a first-line CDK4/6 [inhibitor],” she said. “It’s really a very rare patient in whom I’m not using that in the first line; perhaps an elderly patient in a skilled nursing facility where it’s very cumbersome for her to have laboratory monitoring. However, outside of a situation like that, I’m using a CDK4/6 [regimen] in all my patients.”

Although, cross-study comparisons and head-to-head trials are not feasible for these agents, investigators conducted a match-adjusting indirect comparison (MAIC) study of...
quality-of-life (QOL) outcomes for ribociclib plus an aromatase AI vs abemaciclib plus AI in the first-line treatment of this patient population.4

“I thought this was an interesting paper because biostatisticians have always taught us not to do cross-trial comparisons, and yet they come up with this novel technique of MAICs. They can do just that using QOL data,” Mark Pegram, MD, said. “In this case, they use the EORTC QLQ-C30 [European Organization for Research and Treatment of Cancer QOL] metric as well as the BR23 [EORTC-breast-cancer specific QOL] questionnaires. Using this statistical method, they were able to compare the difference in adverse event [AE]/patient-reported outcomes with these metrics.”

Specifically, the trial compared outcomes from the phase 3 MONALEESA-2 (NCT01958021) and MONARCH-3 (NCT02246261) trials evaluating ribociclib and abemaciclib, respectively. Matching and weighting of individual patient data was performed and 205 and 149 patients in the ribociclib and placebo arms for MONALEESA-2 were matched to 328 and 165 patients in the corresponding arms of MONARCH-3.

Time to first symptom deterioration (TTSD) was significantly better in terms of appetite loss (HR, 0.46; 95% CI, 0.27-0.81), diarrhea (HR, 0.42; 95% CI, 0.23-0.79), fatigue (HR, 0.63; 95% CI, 0.41-0.96) and arm symptoms (HR, 0.49; 95% CI, 0.30-0.79) in those who received the ribociclib-containing regimen vs the abemaciclib regimen. These AEs have been identified by patients as having a moderate to severe effect on their QOL.

“None of this comes as any surprise,” Pegram said. “It’s gratifying to see that the patient-reported outcomes match the investigator-reported data that’s already been published and approved by the FDA for both drugs. [The results] met what I expected, having used these drugs and heard my patients tell me about their experience. That’s gratifying, and I thought the methods were very interesting and novel to allow this kind of cross-trial comparison where a head-to-head trial is simply not available.”

Rugo noted that overall survival (OS) outcomes for abemaciclib are still maturing, but that progression-free survival (PFS) data have demonstrated significant clinical benefit.

**A Closer Look at Ribociclib**

Updated OS results from MONALEESA-3 (NCT02422615), which evaluated ribociclib in the first line setting for postmenopausal patients with advanced hormone receptor-positive, HER2-negative advanced breast cancer, were presented at the ESMO Breast Cancer Congress 2022.5

At a median follow-up of 70.8 months, patients who received ribociclib plus fulvestrant (n = 484) had a median OS of 67.6 months vs 51.8 months among those who were given fulvestrant/placebo (n = 242; HR, 0.67; 95% CI, 0.50-0.90). The 5-year OS rates were 56.5% vs 42.1%, respectively. The experimental combination also delayed time to second disease progression and improved chemotherapy-free survival vs placebo plus fulvestrant (**TABLE**).3

“That [survival is] more than 5 years—an OS we’ve never seen before—as compared with the control group, which was about 51 months,” Pegram said. “This corresponded to a hazard ratio of 0.67. Clear OS advantage is seen with ribociclib plus fulvestrant in the first-line setting.”

Dose reductions with ribociclib were another topic of discussion for the panel. Data from a poster presented during the 2022 ASCO Annual Meeting showed that dose modifications of ribociclib did not demonstrate a negative effect on OS in MONALEESA-2. Trial protocol allowed reductions to 400 mg or 200 mg per day to manage treatment related-AEs.6

**TABLE. Outcomes in MONALEESA-3**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ribociclib/fulvestrant (n = 484)</th>
<th>Placebo/fulvestrant (n = 242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>67.6</td>
<td>51.8</td>
</tr>
<tr>
<td>5-year OS rate</td>
<td>56.5%</td>
<td>42.1%</td>
</tr>
<tr>
<td>Median PFS2, months</td>
<td>50.7</td>
<td>34.6</td>
</tr>
<tr>
<td>Median CFS, months</td>
<td>49.2</td>
<td>29.0</td>
</tr>
</tbody>
</table>

CFS; chemotherapy-free survival; OS, overall survival; PFS2, time to second disease progression.

Among the 334 evaluable patients, 125 did not require a dose reduction (37.4%), 124 patients required 1 reduction (37.1%), 76 required 2 (22.9%), and 9 required more 3 or more (2.7%). The median OS among those who had at least 1 reduction 3 months into treatment was 63.1 months compared with 65.7 months among those with 0 reductions during that time frame (HR, 0.96; 95% CI, 0.68-1.36).4

“In the poster discussion at ASCO 2022, [an audience member] asked, ‘Why don’t you just start at a lower dose? Why start at a higher dose, after all?’” Rugo said. “I thought: Why not just start at the full dose because you can dose-reduce so easily?”

Pegram agreed, saying, “Unless we have randomized data, 400 mg vs 600 mg, I would not start with 400 mg. I would start with 600 mg, but if a patient has an AE, particularly neutropenia, I feel comfortable reducing to 400 mg.”

**Palbociclib**

Data presented at the 2022 ASCO Annual Meeting did not demonstrate a significant improvement with palbociclib plus letrozole vs letrozole alone in the phase 3 PALMOA-2 trial (NCT01740427).7

At the November 15, 2021, data cutoff, at a median follow-up of 90 months, patients...
who received the CDK4/6 inhibitor palbociclib plus letrozole (n = 444) had a median OS of 53.9 months (95% CI, 49.8-60.8) compared with 51.2 months (95% CI, 43.7-58.9) for patients who received placebo plus letrozole (n = 222; HR, 0.956; 95% CI, 0.777-1.177; P = .3378). However, in a post-hoc sensitivity analysis that adjusted for missing survival data, the median OS for patients treated with the combination (n = 385) was 51.6 months (95% CI, 46.9-57.1) compared with 44.6 months (95% CI, 37.0-52.3) for the 175 patients in the control arm (HR, 0.869; 95% CI, 0.706-1.069). The median duration of treatment was 22.0 months and 13.8 months, respectively.

“We saw the long-awaited survival data from PALOMA-2 with disappointing results. There was no difference in the OS, but there were several unique characteristics of PALOMA-2 that are worth keeping in mind,” Rugo said. “One is it’s the only trial in the first-line setting that included patients who had a disease-free interval [DFI] from early- to late-stage disease of less than 12 months. That represented about one-third of the population. In that group of patients, when you look at a forest plot and divide the numbers up, they didn’t clearly have a survival benefit, but among those with a DFI of greater than 12 months—the OS numbers are close to first-line ribociclib and an AI, being well over 60 months.” Specifically, among patients with a DFI greater than 12 months, the median OS was 64.0 months (95% CI, 49.2-73.4) vs 44.6 months (95% CI, 37.0-53.2) with letrozole alone (HR, 0.736; 95% CI, 0.551-0.982).7

Both arms of the trial had significant amounts of missing survival data, Rugo noted. Results were missing for 59 patients in the palbociclib plus letrozole arm and for 47 patients in the letrozole monotherapy. Most patients in both arms had died at the time of the analysis (62% and 60%, respectively). Patients were still alive at a rate of 25% and 19%, respectively. “A lot of patients withdrew consent for reasons that are unclear, and so they just didn’t have survival data on those patients, unfortunately,” she said. “PALOMA-1 [NCT00721409] opened the field of CDK4/6 inhibitors,” Aditya Bardia, MD, MPH, said. “Since then, we’ve had several studies. In terms of why the results of PALOMA-2 were negative [although] we are seeing positive results from MONALEESA-2, MONALEESA-3, MONALEESA-7 [NCT02278120], and MONARCH-2, I think this could be differences in study populations [or other causes]. The DFI [subset] was different, the results looked similar. The second possibility is what happened after the patients had disease progression on first-line therapy. That was not controlled, so there could be some imbalances in the placebo vs the palbociclib arm. The third possibility is that there are some differences in the drug; it’s just impossible to know without head-to-head trial comparison.”

O’Dea noted that in clinical practice she has observed patients exhibiting prolonged clinical benefit on palbociclib. “If we look at the entire PALOMA series, we see the dramatic efficacy of this drug; 10% of patients continue on palbociclib at 7.5 years,” she said. “I certainly have a couple of patients in my own clinic that started the drug in February of 2015 and remain on the drug today. Clearly, it’s an effective agent…. There are a lot of nuances to this.”

Bardia agreed adding that although the PALOMA-2 data were not significant, if a patient is currently on palbociclib, he would feel very comfortable continuing treatment. However, for new patients with metastatic disease, he would consider the evidence from other trials in treatment selection.

WILL REAL-WORLD OUTCOMES INFORM FUTURE DIRECTIONS?

In selecting between agents in the first-line setting, Pegram said that there are 2 vantage points when reviewing the data: clinical vs scientific. “From a clinical perspective, we have level 1 evidence from a randomized, controlled phase 3 trial of an OS benefit that’s statistically significant in the case of the first-line ribociclib plus AI. That is the gold standard for clinical decision-making. For clinical decisions, that’s impactful to me,” he said. “The other perspective I like to look at this data set from is more from a scientific point of view. From that point of view, things are a little bit less clear.”

Considering real-world data may shine a light on certain pathways forward for patients in this setting. “We talked about patient populations in clinical trials, which is always going to be contrived; there’s no way around it,” Rugo said, adding that inclusion criteria for different trials have a huge effect on outcomes. “You really are treating a different patient population [in the clinic] with a different biology of tumor in many situations. There’s quite a lot of real-world data on CDK4/6 inhibitors and then there’s also some data about how AEs are managed in routine clinical practice.”

At the ESMO Breast Cancer Congress 2022, Rugo presented a poster on the real-world outcomes for patients treated with palbociclib plus endocrine therapy.8 In a retrospective analysis 1324 patients were identified for palbociclib plus endocrine therapy vs 1564 with an AI alone. The median OS was 53.4
(95% CI, 48.7-58.6) vs 40.4 months (95% CI, 36.3-44.9), respectively (HR, 0.67; 95% CI, 0.60-0.76; P < .0001).

“If you look at the results, they are quite similar to the other clinical trials with ribociclib and even abemaciclib in the sense that you see an improvement in OS,” Bardia said “We must be careful in terms of interpreting real-world data. It was not a randomized trial. But at least there’s evidence that it improved OS.”

Data from another retrospective study, REACH AUT, showed that the efficacy of ribociclib in the phase III MONALEESA trials. At a median follow-up of 14.4 months, 283 patients treated with ribociclib plus an aromatase inhibitor (AI) vs AI in metastatic breast cancer: a large real-world database analysis. Am Oncol. 2022;33(suppl 3):S194. doi:10.1016/j.annonc.2022.03.188

In reviewing all the data, treatment selection in clinical practice may lean heavier on the level of toxicity [with a given treatment].”

“Ultimately, a good balance of tolerability, QOL, and the efficacy data as we have; we can have a discussion with our patient.”

REFERENCES
5. Neven P, Fasching PA, Chia S, et al. Updated overall survival (OS) results from the first-line (1L) population in the phase III MONALEESA-3 trial of postmenopausal patients (PTS) with HR+/-HER2− advanced breast cancer (ABC) treated with ribociclib (RBC) + fulvestrant (FUL). Am Oncol. 2022;33(suppl 3):S217. doi:10.1016/j.annonc.2022.03.280
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.
For appropriate patients faced with 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 on treatment, 9% were in follow-up, and 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

**Visual Acuity Changes:** A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 14% of patients. 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 the 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 30%, 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 1 in 13%, Grade 2 in 3%, 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.

**USE IN SPECIFIC POPULATIONS**

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

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

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

**Renal or Hepatic Impairment:** The recommended dosage has not been established in patients with severe renal impairment (eGFR <15 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.**
5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

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

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

5.3 Thrombocytopenia

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

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fetal 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 pemphigus for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

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

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 1.3)].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2.

Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

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

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (5%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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

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

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Keratopathya</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuityb</td>
<td>53</td>
</tr>
<tr>
<td>Blurred visionc</td>
<td>22</td>
</tr>
<tr>
<td>Dry eyesa</td>
<td>14</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatiguec</td>
<td>20</td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactionsb</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>11</td>
</tr>
</tbody>
</table>

- a Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.
- b Decreased visual acuity included diplopia, vision blurred, visual acuity reduced, and visual impairment.
- c Dry eyes included dry eye, ocular discomfort, and eye pruritus.
- d Fatigue included fatigue and asthenia.
- e Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthma, hypertension, lethargy, tachycardia.
- f 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. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

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

### 6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology 13.1), and 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 75% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has 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 [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
Advises the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Toxicity
• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].
• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS
BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:
• Patients must complete the enrollment form with their provider.
• Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia
• Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions
• Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity
• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].
• Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].
• Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation
• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

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

Trademarks are owned by or licensed to the GSK group of companies.
Manufactured by:
GSK
Research Triangle Park, NC 27709
©2020 GSK group of companies or its licensor.
August 2020 BRP-1BRS
©2021 GSK or licensor.
BLMADVT190001 January 2021
Produced in USA.
Tumor Agnostic Role of TMB Biomarker Faces Challenges

by JANE DELARTIGUE, PhD

ALTHOUGH TUMOR MUTATIONAL burden (TMB) is established as a clinically informative feature of tumors, its optimal use in therapeutic decision-making faces many challenges, and we are only beginning to fully understand its strengths and limitations. Development of biomarkers that can be readily applied in the clinic to identify patients most likely to respond to groundbreaking immunotherapies has become a priority in immuno-oncology. ¹

Next-generation sequencing (NGS), used to estimate the number of somatic mutations within a tumor specimen, is among the leading candidates for TMB detection. The pinnacle of its success arrived in mid-2020 with the tumor agnostic FDA approval of the immune checkpoint inhibitor (ICI) pembrolizumab (Keytruda) for patients with high TMB. ² New studies evaluating the pANCancer role of TMB as a predictive biomarker of response to ICIs have revealed some of its limitations, raising doubts about its broad applicability and the appropriateness of a universal TMB cutoff. ³⁻⁶

In non–small cell lung cancer (NSCLC), the predictive power of TMB is perhaps best characterized, these challenges present a hurdle to clinical implementation of TMB assays. A supplemental biologics license application for the dual checkpoint inhibition in patients with NSCLC who had high TMB was subsequently withdrawn by the drug developers when a phase 3 trial failed to demonstrate an overall survival (OS) benefit in this population. ⁷⁻⁸ Ongoing research is focused on finding ways to unleash the true potential of TMB, including efforts to standardize its measurement, define better cutoffs, and understand its role in common cancer types that have been largely overlooked. ⁹⁻¹⁰

THE MORE, THE MERRIER?

In 2017, pembrolizumab received an historic tumor agnostic approval for the treatment of tumors with high levels of microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) after these biomarkers were shown to identify patients with improved outcomes. ¹¹ The theory behind the efficacy of ICIs in this patient population was that tumors with greater numbers of mutations provoke a stronger anti-tumor immune response because they increase the presence of neoantigens, which activate cytotoxic T cells, on the tumor cell surface. ¹²⁻¹³ Mismatch repair (MMR) is a mechanism through which cells repair types of DNA damage that typically occur within areas of short, repetitive DNA sequences known as microsatellites. Abnormalities in the MMR pathway lead to inability to repair damaged DNA and accumulation of mutations, as well as a characteristic variability in the lengths of microsatellites; thus, MSI-H is an indication of dMMR. ¹⁴ Although dMMR/MSI-H is more common in some tumors than others, it is observed in a small proportion of patients overall. ¹⁵ Although almost all tumors with MSI-H have high mutation rates, less than one-fifth of highly mutated tumors display MSI-H, suggesting that other mechanisms drive some tumors to acquire more mutations. ¹⁶

Assessment of TMB using whole-exome sequencing (WES) allowed investigators to capture highly mutated tumors irrespective of cause; although TMB varies, a subset of patients with high TMB can be observed in almost every cancer type. ¹⁶ Initial retrospective studies in NSCLC and melanoma demonstrated that higher levels of TMB were associated with improved outcomes following ICIs. ¹⁷⁻¹⁹ Since then, TMB has emerged as a powerful predictor of response to ICIs across different cancer types. ³⁻⁹

Targeted NGS panels, which are faster and less expensive than WES, provide a comparable estimate of TMB and are widely used. ¹⁹⁻²¹ Most measure TMB from tissue biopsies, but liquid biopsies that use circulating tumor DNA isolated from the blood are being developed. ⁷ A growing number of prospective trials have been initiated to validate the relationship between TMB and ICI outcomes. Most notable is the phase 2 KEYNOTE-158 trial (NCT02628067), in which pembrolizumab monotherapy was evaluated in patients with multiple types of advanced solid tumors that had progressed following prior treatment. Among 102 patients with high levels of TMB (≥ 10 mutations [mut]/Mb), the overall response rate (ORR) was 29.4% (95% CI, 20.8%-39.3%), with complete responses in 4 patients and 57% of responses lasting at least 12 months. Responses were observed across 8 tumor types. An ORR of 6.3% (95% CI, 4.6%-8.3%) was observed in patients with TMB lower than 10 mut/Mb (n = 688). ²
These results led the FDA to approve pembrolizumab in June 2020 for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high (≥ 10 mut/Mb) solid tumors, securing another tumor agnostic win for the drug. The FoundationOne CDx assay, a 324-gene panel that estimates TMB based on a 0.8 Mb region of the exome, was approved as a companion diagnostic for use in this indication.2

Although FoundationOne CDx is the only FDA-approved TMB assay, Memorial Sloan Kettering Cancer Center in New York, New York, developed MSK-IMPACT, which leverages a 468-gene panel covering a 1.1-Mb region of the exome and has been authorized by the FDA through the 510K pathway. Numerous other TMB assays are commercially available for use in a research setting (Table).22

The abundance of available assays has led to questions surrounding standardization of TMB estimation across different assays and tumor types. Friends of Cancer Research established a TMB Harmonization Consortium of stakeholders from pharmaceutical and diagnostic companies and scientific organizations, including the FDA, to conduct a comprehensive review of available data regarding TMB and response to immunotherapy.

They found that some assays consistently underestimated TMB and others overestimated, compared with WES-derived TMB, with the size and content of the gene panel identified as key factors in assay performance. They developed a calibration tool to enhance the comparability of assays.23,24

### POTENTIAL PITFALLS

Doubts remain regarding the broad applicability of TMB as a predictive biomarker and over the use of a universal cutoff for determining high TMB. A criticism of KEYNOTE-158 is that it did not include more common tumor types, such as colorectal cancer, prostate, and breast cancer.10

The predictive role of TMB is being explored in these settings. Prostate cancer is notable considering that ICIs typically offer little benefit to most patients. Preliminary data presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium demonstrated that a cohort of patients with advanced prostate cancer who received ICI therapy guided by blood-based TMB score experienced clinical benefit.23 In a separate real-world biomarker study, investigators showed that patients with metastatic castration-resistant prostate cancer who had high TMB (≥ 10 mut/Mb) derived greater benefit from ICIs vs taxane chemotherapy.23

Another issue with KEYNOTE-158 is that among the tumor types enrolled, TMB appeared to be a better predictor of response in only some tumors. For example, the ORR in patients with endometrial cancer was 47%, compared with 7% in patients with anal cancer.2

Additionally, the study measured ORR and not more clinically meaningful end points. Several subsequent studies have now evaluated the relationship between patient survival and TMB. Samstein et al analyzed the clinical and genomic data of 1662 patients with advanced cancer treated with ICIs whose tumors were evaluated for TMB using the MSK-IMPACT assay. High TMB (defined as the highest 20% in each tumor type) was associated with improved OS across most cancer types, although in some cases not statistically significantly.3

A notable exception was glioma, in which high TMB was associated with poorer survival,7 possibly because the high TMB observed in glioma may result from treatment with DNA-damaging cytotoxic drugs and may not necessarily be associated with increased infiltration of T cells into the tumor microenvironment. Another study demonstrated an association between TMB and improved OS following ICI therapy, but only among tumors in which the levels of CD8-positive T cells correlated with predicted neoantigen load, such as melanoma, lung cancer, and bladder cancer.7

In a third study examining the relationship between TMB and post-ICI OS, which used the approved cutoff of 10 mut/Mb, the median OS was longer only in patients with certain types of MMR-proficient cancer, such as head and neck cancer, NSCLC, and melanoma, with no benefit in patients with other cancer types.4 These results have led some to argue that the clinical benefit of high TMB as a biomarker has not been convincingly demonstrated across all tumor histologies.10

Another challenge to the clinical application of TMB assays is how to define an appropriate cutoff for high TMB. In their study, Samstein et al found that the top 20% of TMB varied markedly between cancer types.1 In another study, investigators sought to determine how the FDA-approved cut-off performed in a real-world setting. They analyzed the outcomes of more than 1600 patients treated with ICIs.

Overall patients with a TMB of at least 10 mut/Mb had better outcomes than those with a TMB below 10 mut/Mb; the universal cutoff did not reliably predict increased survival after immunotherapy across all tumor types. Notably, in patients with renal cell carcinoma, no cases met the high TMB threshold but many patients still responded.4 Many argue that a cancer type-specific threshold may be better, whereas others have suggested that an arbitrary threshold of high TMB is wholly inappropriate and that the use of ICIs should instead be considered in the context of the cause of the TMB.5,6

### TMB IN NSCLC

The greatest preponderance of data showing an association between TMB and ICI response comes from NSCLC, but even in this setting its predictive role remains uncertain. Subgroup analyses from randomized clinical trials of ICIs in NSCLC in various settings demonstrated significantly improved response rates and progression-free survival (PFS) in patients with high TMB compared with those with low TMB when ICIs were used as monotherapy.27,28

---

**TABLE. Select Commercially Available NGS Panels for Estimation of TMB**22

<table>
<thead>
<tr>
<th>Panel</th>
<th>Developer</th>
<th>Number of genes</th>
<th>Region covered (Mb)</th>
<th>Type of mutations included</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTOncom®</td>
<td>ACT Genomics</td>
<td>440</td>
<td>1.12</td>
<td>NS, S</td>
</tr>
<tr>
<td>Caris Molecular Intelligence</td>
<td>Caris Life Science</td>
<td>592</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>FoundationOne CDx®</td>
<td>Foundation Medicine</td>
<td>324</td>
<td>0.80</td>
<td>NS, S</td>
</tr>
<tr>
<td>FoundationOne Liquid CDx®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GuardantOMNI®</td>
<td>Guardant Health</td>
<td>500</td>
<td>1.00</td>
<td>NS, S</td>
</tr>
<tr>
<td>MSK-IMPACT®</td>
<td>Memorial Sloan Kettering</td>
<td>468</td>
<td>1.14</td>
<td>NS</td>
</tr>
<tr>
<td>NestTYPE Discovery Profile</td>
<td>NeoGenomics</td>
<td>323</td>
<td>1.03</td>
<td>NS, S</td>
</tr>
<tr>
<td>for Solid Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncomine Tumor Mutation Load</td>
<td>Thermo Fisher Scientific</td>
<td>409</td>
<td>1.20</td>
<td>NS</td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGDx elio tissue complete®</td>
<td>Personal Genome Diagnostics</td>
<td>507</td>
<td>1.33</td>
<td>NS, S</td>
</tr>
<tr>
<td>QIAspec TMB panel</td>
<td>QIAGEN</td>
<td>486</td>
<td>1.33</td>
<td>NS, S</td>
</tr>
<tr>
<td>TruSight Oncology 500</td>
<td>Illumina</td>
<td>523</td>
<td>1.33</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, nonsynonymous; S, synonymous; TMB, tumor mutational burden.

*FDA-approved companion diagnostic for use in assessing TMB.

**Blood-based diagnostic that measures TMB from circulating tumor DNA contained within the plasma.

**Diagnostic cleared by the FDA through the 510K pathway.

---

**TMB, CONTINUED ON PAGE 44**
OncLive® is a podcast from OncLive®, which provides oncology professionals with the resources and information they need to provide the best patient care. In both digital and print formats, OncLive® covers every angle of oncology practice, from new technology to treatment advances to important regulatory decisions.

TUNE IN!

In our exclusive interview, Vivek Subbiah, MD, discusses the FDA approval of dabrafenib (Tafinlar) plus trametinib (Mekinist) in solid tumors with BRAF V600E mutation.
The Network

**MUTATIONS LEAVE THEIR MARK ON TUMORS**

**THE ADVENT OF GENOME** sequencing has permitted investigators to examine the mutational landscapes of cancer and revealed that not only do types of mutations associated with tumorigenesis vary across types of cancer, but so does the number of mutations.1-3

Through whole-exome sequencing, the total number of mutations present within a tumor specimen, known as tumor mutational burden (TMB), can be measured and is typically expressed as the number of mutations (mut) per megabase (Mb) of coding DNA. TMB varies widely among tumor types, ranging from 0.1 mut/Mb in some pediatric tumors to around 100 mut/Mb in melanoma and lung cancer.1-3

Various underlying causes of higher mutational load have been identified; certain environmental carcinogens (ie, chronic exposure to tobacco smoke or UV radiation) are associated with higher mutational load, as are alterations in genes that orchestrate DNA replication or DNA damage repair.1 In the past decade, a series of groundbreaking studies has unveiled a potential link between high mutational load and antitumor immune response, which seems to have implications for response to cancer immunotherapy4-6 (FIGURE). Tumors with high TMB have been shown to respond better to immune checkpoint inhibitors (ICIs). The reasons for this phenomenon are still being explored, but the current thinking is that a greater number of mutations makes the tumor more visible to the immune system.1,4

Some mutations can give rise to abnormal proteins that may be targeted for degradation by the immunoproteasome, a specialized type of proteasome activated by inflammatory stimuli that are common in the tumor microenvironment. The immunoproteasome breaks down abnormal or nonself proteins and processes them into neoantigens, which are then presented by major histocompatibility complex class I molecules on the cell surface where they can induce activation of cytotoxic T cells.6-9

ICIs target immune checkpoint proteins, principally the PD-1 protein and its receptor PD-L1, which play a key role in immune tolerance, suppressing the immune response to self-antigens and preventing damage to healthy tissue. These same tolerance mechanisms can be exploited by tumors to elude the antitumor immune response; PD-L1 is often overexpressed on the surface of tumor cells and engages the PD-1 receptor on activated T cells that infiltrate the tumor space, switching them off.10

ICIs block the interaction between PD-1 and its receptor, thwarting this mechanism of immune evasion. However, their activity is predicated upon an active antitumor immune response, and this is where mutational load comes into play.11 The greater the number of mutations a tumor has, the greater the likelihood it will express neoantigens on its surface and trigger an antitumor immune response.12

Patients with advanced/metastatic NSCLC who were treated with pembrolizumab plus chemotherapy in biomarker-selected patients achieved significantly longer median progression-free survival (PFS) compared with those who received chemotherapy alone.13-15 In the pembrolizumab arm, the median PFS was 9.6 months (95% CI, 8.8-12.2) vs 2.8 months (95% CI, 1.6-5.6) in the chemotherapy arm. Similarly, the median OS was 23.6 months (95% CI, 19.8-37.5) vs 10.3 months (95% CI, 7.4-15.8) in the pembrolizumab arm vs the chemotherapy arm, respectively.15

In B-FAST, in which atezolizumab monotherapy was compared with platinum-based chemotherapy in biomarker-selected patients with advanced NSCLC, results from cohort C, in which patients were selected based upon high TMB levels, failed to meet the primary end point of OS.15-17

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

**FIGURE. Tumor Mutational Burden as an Immunotherapy Biomarker**

InB-F1RST, the primary biomarker end point was investigator-assessed PFS at the cutoff of bTMB of at least 16. The median PFS was 5 months (95% CI, 1.6-10.8) in patients with high TMB compared with 3.5 months (95% CI, 2.6-4.3) for those with low TMB (HR, 0.80; 90% CI, 0.54-1.18; P = .39). The median OS was 23.9 months (95% CI, 18.8-not estimable) vs 13.4 months (HR, 0.66; 90% CI, 0.40-1.10; P = .18), respectively. Further, the ORR in the bTMB-high group was 35.7% (95% CI, 19.2%-55.5%) vs 5.5% in the bTMB-low group (95% CI, 2.2%-12.2%) (P < .0001). In B-FAST, in which atezolizumab monotherapy was compared with platinum-based chemotherapy in biomarker-selected patients with advanced NSCLC, results from cohort C, in which patients were selected based upon high bTMB levels, failed to meet the primary end point of PFS.15-17

Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.

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

---

However, its predictive role in patients receiving ICIs in combination with chemotherapy appears more limited; in the KEYNOTE-189 (NCT02578680) study, high TMB was not significantly associated with improved OS, PFS or ORR in patients treated with pembrolizumab plus chemotherapy as first-line therapy for metastatic nonsquamous NSCLC.17

Foundation Medicine’s blood-based TMB assay was being used in the phase 2/3 B-F1RST (NCT02848651) and phase 3 B-FAST (NCT03178552) trials, which evaluated the potential of TMB as a predictive biomarker for atezolizumab (Tecentriq) in the frontline treatment of advanced/metastatic NSCLC. High TMB (defined as 14.5 mut/Mb) was measured as 16 or greater in the blood TMB (bTMB) scale.

In B-F1RST, the primary biomarker end point was investigator-assessed PFS at the cutoff of bTMB of at least 16. The median PFS was 5 months (95% CI, 1.6-10.8) in patients with high TMB compared with 3.5 months (95% CI, 2.6-4.3) for those with low TMB (HR, 0.80; 90% CI, 0.54-1.18; P = .39). The median OS was 23.9 months (95% CI, 18.8-not estimable) vs 13.4 months (HR, 0.66; 90% CI, 0.40-1.10; P = .18), respectively. Further, the ORR in the bTMB-high group was 35.7% (95% CI, 19.2%-55.5%) vs 5.5% in the bTMB-low group (95% CI, 2.2%-12.2%) (P < .0001). In B-FAST, in which atezolizumab monotherapy was compared with platinum-based chemotherapy in biomarker-selected patients with advanced NSCLC, results from cohort C, in which patients were selected based upon high bTMB levels, failed to meet the primary end point of PFS.15-17

Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.

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

---

**TMB, CONTINUED FROM PAGE 42**

However, its predictive role in patients receiving ICIs in combination with chemotherapy appears more limited; in the KEYNOTE-189 (NCT02578680) study, high TMB was not significantly associated with improved OS, PFS or ORR in patients treated with pembrolizumab plus chemotherapy as first-line therapy for metastatic nonsquamous NSCLC.17

Foundation Medicine’s blood-based TMB assay was being used in the phase 2/3 B-F1RST (NCT02848651) and phase 3 B-FAST (NCT03178552) trials, which evaluated the potential of TMB as a predictive biomarker for atezolizumab (Tecentriq) in the frontline treatment of advanced/metastatic NSCLC. High TMB (defined as 14.5 mut/Mb) was measured as 16 or greater in the blood TMB (bTMB) scale.

In B-F1RST, the primary biomarker end point was investigator-assessed PFS at the cutoff of bTMB of at least 16. The median PFS was 5 months (95% CI, 1.6-10.8) in patients with high TMB compared with 3.5 months (95% CI, 2.6-4.3) for those with low TMB (HR, 0.80; 90% CI, 0.54-1.18; P = .39). The median OS was 23.9 months (95% CI, 18.8-not estimable) vs 13.4 months (HR, 0.66; 90% CI, 0.40-1.10; P = .18), respectively. Further, the ORR in the bTMB-high group was 35.7% (95% CI, 19.2%-55.5%) vs 5.5% in the bTMB-low group (95% CI, 2.2%-12.2%) (P < .0001). In B-FAST, in which atezolizumab monotherapy was compared with platinum-based chemotherapy in biomarker-selected patients with advanced NSCLC, results from cohort C, in which patients were selected based upon high bTMB levels, failed to meet the primary end point of PFS.15-17

Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.

For a full list of references, see the article at OncLive.com
Osimertinib/Savolitinib Combo Looks to Overcome Acquired Resistance in EGFR-Mutant NSCLC

by BRITTANY LOVELY

ACQUIRED RESISTANCE DUE TO genetic alterations in the MET receptor has limited the efficacy of the EGFR inhibitor osimertinib (Tagrisso) in patients with non–small cell lung cancer (NSCLC). Investigators have sought to circumvent this barrier through targeting MET protein activity with the addition of the novel MET tyrosine kinase inhibitor (TKI), savolitinib.1

“Osimertinib is the preferred first-line treatment in EGFR-mutant advanced NSCLC; however, tumors can develop resistance,” investigators wrote in a poster presented at the 2022 International Association for the Study of Lung Cancer World Conference on Lung Cancer Annual Meeting.2 “MET overexpression and/or amplification is the most common resistance mechanism to osimertinib; despite this, there is no approved targeted therapy for these patients. Platinum-based chemotherapy remains the standard of care, with limited efficacy.”

A preliminary efficacy analysis of the combination of savolitinib plus osimertinib demonstrated an improvement in outcomes among patients with EGFR-mutant NSCLC with MET overexpression following disease progression on osimertinib.1 Investigators of the phase 2 SAVANNAH study (NCT03778229) performed a baseline analysis for MET overexpression and amplification using immunohistochemistry (IHC; 3+ in ≥ 50% of tumor cells) and fluorescence in situ hybridization (FISH; MET copy number ≥ 5 and/or MET:CEP7 signal ratio ≥ 2), respectively.1

Overexpression and amplification in the overall population were IHC50+ and FISH5+, respectively. Subgroup analyses were performed among patients with or without IHC90+ and FISH10+, respectively.

At data cutoff, 196 patients had been treated and 193 were available for efficacy evaluation. Patients received oral savolitinib 300 mg twice daily in combination with oral osimertinib 80 mg once daily. The objective response rate (ORR) was 32% (95% CI, 26%-39%), with a median duration of response (DOR) of 8.3 months (95% CI, 6.9-9.7); the disease-control rate was 61% (95% CI, 53%-68%). The median progression-free survival (PFS) was 3.3 months (95% CI, 4.2-5.8).1

Among patients with IHC90+ and/or FISH10+ (n = 108), the ORR was 49% (95% CI, 39%-59%), with a median DOR of 9.3 months (95% CI, 7.6-10.6). The DCR was 74% (95% CI, 65%-82%), and a median PFS was 7.1 months (95% CI, 5.3-8.0). Investigators noted that although the DOR is not fully mature, with a median follow-up of 13 months, the responses in this subgroup appear to be durable.1

A reduced clinical benefit was observed among patients without ICH90+ and/or FISH10+ status (n = 77). The ORR was 9% (95% CI, 4%-18%) with a median DOR of 6.9 months (95% CI, 4.1-16.9). The DCR was 43% (95% CI, 32%-55%) and the median PFS was only 2.8 months (95% CI, 2.6-4.3).

Among 196 patients in the safety analysis set (n = 196), the median age was 63 years (range, 34-86) and 62% were women. Most patients had an ECOG performance status of 1 (63%) and no central nervous system involvement at study entry (66%).

Adverse effects (AEs) of any grade were reported among 99% of patients, with 84% of AEs related to any study treatment. Grade 3 or higher AEs were reported among 45% of patients, with 20% of patients experiencing grade 3 or higher AEs related to study treatment. Serious AEs were reported in 29% of patients, 7% of which were related to the study treatment.

Twenty-six patients discontinued treatment due to AEs related to savolitinib and 21 patients due to osimertinib AEs. The median duration of treatment with savolitinib was 4.8 months (range, 0.1-25.7) and was 4.9 months (range, 0.1-25.7) with osimertinib.

The most common grade 3 or higher AEs were pulmonary embolism (5%), dyspnea (4%), decreased neutrophil count (4%), pneumonia (4%), hyperalbinemia (2%), pleural effusion (2%), vomiting (2%), and anemia (2%).

Further, 1 patient each reported grade 3 or higher hypersensitivity and interstitial lung disease/pneumonitis, respectively.

INVESTIGATORS PUSH MET/EGFR INHIBITION TO PHASE 3

Leveraging the improved outcomes from SAVANNAH, investigators have initiated the phase 3 SAVFRRON trial (NCT05261399). The randomized study will evaluate the safety and efficacy of savolitinib in combination with osimertinib vs standard-of-care platinum doublet chemotherapy.2 The primary end point is PFS, with secondary end points of overall survival, ORR, DOR, DCR, time to discontinuation, and tumor shrinkage (FIGURE).2

Eligibility for enrollment requires that patients have EGFR-mutant, MET-overexpressed or -amplified, locally advanced or metastatic NSCLC who have disease progression on first- or second-line osimertinib.2 Disease progression must have occurred less than 6 months after the last dose if osimertinib was administered in the adjuvant setting. Patients must be 18 years or older, expect in Japan where the minimum age for enrollment is 20 years.

Individuals are not eligible if they have active gastrointestinal disease, selected cardiac diseases, severe or uncontrolled systemic disease, active infections, and/or liver disease. Those with predominant squamous cell histology and symptomatic brain metastases are also ineligible.

Stratification factors include second- vs third-line therapy, baseline brain metastases (yes vs no), and race (Asian vs non-Asian). Upon disease progression, investigators can determine whether patients will continue to receive treatment with the combination or osimertinib monotherapy if a clinical benefit is observed.

The primary analysis of the study is expected in June 2025.2
**INDICATION**

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab

In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

There are no contraindications for LYNPARZA.

**WARNINGS AND PRECAUTIONS**

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):

Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis:

Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity:

Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

**ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab**

Most common adverse reactions (Grades 1-4) in ≥10% of patients treated with LYNPARZA/bevacizumab compared to a ≥5% frequency for placebo/bevacizumab in the first-line maintenance setting for PAOLA-1 were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%) and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency...
**PAOLA-1**

~50% WERE HRD POSITIVE

### PRESPECIFIED EXPLORATORY ANALYSIS\(^1,3\): 

![Image](image_url)

**LYNPARZA + BEVACIZUMAB**

**BEVACIZUMAB + PLACEBO**

Median PFS was 37.2 months with LYNPARZA + bevacizumab (n=255) and 17.7 months with bevacizumab + placebo (n=132); HR=0.33; 95% CI: 0.25–0.45\(^1\)

*Data based upon a prespecified exploratory subgroup analysis, which was not controlled for Type 1 error. HRD status was not a stratification factor in PAOLA-1.* \(^3\)

### STUDY DESIGN\(^1,3\)

PAOLA-1 was a phase 3 trial of women with advanced ovarian cancer that enrolled patients regardless of surgical outcome or BRCA mutation status following response to first-line platinum-based chemotherapy with bevacizumab. Patients were randomized 2:1 (N=806) to receive LYNPARZA tablets 300 mg BID in combination with bevacizumab 15 mg/kg (n=537) or placebo BID in combination with bevacizumab 15 mg/kg (n=269).

Bevacizumab was administered every 3 weeks for a total duration of up to 15 months, and LYNPARZA or placebo treatment was administered for up to 24 months or until disease progression or unacceptable toxicity.

The primary endpoint was the investigator-assessed PFS. Prespecified exploratory analyses included PFS in predefined subgroups, including HRD status and BRCA mutation status. **PFS within HRD-positive patients served as the basis of the FDA-approved indication.**

---

**IMPORTANT SAFETY INFORMATION (Cont’d)**

Compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%) and headache (14%).

In addition, venous thromboembolic events occurred more commonly in patients receiving LYNPARZA/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Most common laboratory abnormalities (Grades 1–4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the **first-line maintenance setting** for PAOLA-1 were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%) and decrease in platelets (35%).

### DRUG INTERACTIONS

**Anticancer Agents:** Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

**CYP3A Inhibitors:** Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

**CYP3A Inducers:** Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

### USE IN SPECIFIC POPULATIONS

**Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production.

Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

**Pediatric Use:** The safety and efficacy of LYNPARZA have not been established in pediatric patients.

**Hepatic Impairment:** No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

**Renal Impairment:** No dosage modification is recommended in patients with mild renal impairment (Clcr 51–80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (Clcr 31–50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (Clcr ≤30 mL/min).

You are encouraged to report negative side effects of AstraZeneca prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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

BID=twice daily; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; mPFS=median progression-free survival.

**References:**
1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021.

LYNPARZA is a registered trademark of the AstraZeneca group of companies. ©2021 AstraZeneca. All rights reserved. US-53362 S/21
**Adverse Reaction**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza tablets n=260</th>
<th>Placebo n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2 Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza/bevacizumab n=267</th>
<th>Placebo/bevacizumab n=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3 Laboratory Abnormalities Reported in 25% of Patients in SOL01-1**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Lynparza tablets n=260</th>
<th>Placebo n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>Increase in mean corpuscular volume</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>Decrease in leukocytes</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in lymphocytes</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in neutrophils</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Increase in serum creatinine</td>
<td>88</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza/bevacizumab n=267</th>
<th>Placebo/bevacizumab n=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 5**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza tablets n=260</th>
<th>Placebo n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 6**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza tablets n=260</th>
<th>Placebo n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Generalized weakness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>nausea</td>
<td>37</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue</td>
<td>42</td>
</tr>
<tr>
<td>Arm and Shoulder Syndrome</td>
<td>Fatigue</td>
<td>38</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection/infected/inflamed</td>
<td>30</td>
</tr>
<tr>
<td>UTI</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3 Laboratory Abnormalities Reported in 25% of Patients in SOL01-1**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Lynparza tablets n=260</th>
<th>Placebo n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>Increase in mean corpuscular volume</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>Decrease in leukocytes</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in lymphocytes</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in neutrophils</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Increase in serum creatinine</td>
<td>88</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza/bevacizumab n=267</th>
<th>Placebo/bevacizumab n=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 5**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza tablets n=260</th>
<th>Placebo n=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Generalized weakness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>nausea</td>
<td>37</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue</td>
<td>42</td>
</tr>
<tr>
<td>Arm and Shoulder Syndrome</td>
<td>Fatigue</td>
<td>38</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection/infected/inflamed</td>
<td>30</td>
</tr>
<tr>
<td>UTI</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>
Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in Study 19. At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 5.6 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 49% and dose reductions due to an adverse reaction occurred in 27%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anaemia (22%), neutropenia (9%), and fatigue (8%). Dose discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in SOLO-2.

Table 6 Adverse Reactions in SOLO-2 (% of Patients Who Received Lynparza)
CAR T-Cell Therapy Establishes Prominent Role Across Hematologic Malignancies

by ABHINAV DEOL, MD

In recent years, cellular immune therapies such as chimeric antigen receptor (CAR) T-cell therapy have significantly improved response rates for various hematological malignancies. The Multiple Myeloma and Amyloidosis Multidisciplinary Team (MDT), Bone Marrow and Stem Cell Transplant MDT, and the Hematologic Oncology MDT at Barbara Ann Karmanos Cancer Institute in Detroit, Michigan, have helped drive many treatment advancements in cellular immune therapies for cancers.

Karmanos offers all approved CAR T-cell therapies for non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), and multiple myeloma (MM). The institute also continues to support research into new treatment indications for which CAR T-cell therapy could be used. CAR T-cell therapy is at the cutting edge of treatments for certain cancers, wherein the patient’s T cells, an integral part of the immune system, are genetically modified to recognize and kill the cancer cells.

Cancers show promising CAR T response rates

The outcomes of CAR T-cell therapies have been remarkable, especially because most patients receiving this immunotherapy have faced difficulties in controlling their disease despite multiple rounds of chemotherapy. The Karmanos team collaborated with leading cancer centers around the country on various pivotal clinical trials leading to the FDA approval of CAR T-cell therapy.

The complete response rates for ALL are approximately 60% to 70%.1,2 Regarding NHL, the FDA has approved CAR T-cell therapy to treat diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma and transformed lymphoma. Patients with these diseases must meet specific requirements to receive CAR T-cell therapy including that their cancer does not respond to initial chemotherapy and relapses within 1 year or there is relapse after 2 previous lines of chemotherapy.

The long-term complete response rates in patients with DLBCL in the third-line setting are around 40% to 50%.3-5 For patients with DLBCL whose disease does not respond to initial therapy or relapses within 1 year of completing treatment, CAR T-cell therapy significantly improved the chance of being cured compared with standard salvage chemotherapy.6,7

With CAR T-cell therapy, we can also target mantle cell lymphoma. For this disease, we have seen a complete response in two-thirds of patients whose disease had relapsed or not responded to multiple chemotherapy regimens.8 CAR T-cell therapy also showed very high response rates in patients with follicular lymphoma whose disease had relapsed after 2 prior lines of chemotherapy.9,10 The response rate for patients with MM whose disease relapsed after 4 or more prior lines of
chemotherapy was 80% to 95% after CAR T-cell therapy treatment.11,12

POSSIBLE ADVERSE EFFECTS
Some patients may develop unique adverse effects (AEs) that should be monitored closely for the first few weeks after infusion. AEs include cytokine release syndrome (CRS), which may manifest as high fever, low blood pressure, low oxygenation, neurological toxicity, confusion, word-finding difficulty, and rare cases of seizure or coma. The most severe AEs usually occur within the first couple of weeks after infusion of CAR T cells. Patients can also be at risk for low blood counts and a weakened immune system. If this happens, the patient may need antimicrobial treatments to prevent severe infection.

ONGOING CAR T-CELL THERAPY RESEARCH
In the recent years, research has also focused on strategies to reduce the AEs of this unique therapy. Karmanos participated in a clinical trial in which patients with DLBCL received steroids for 3 days at the time of infusion of CAR T-cell therapy, which led to less risk of CRS without compromising efficacy of the treatment.13 This approach is now used for patients at a high risk of developing severe AEs from CAR T-cell therapy.

We have an ongoing clinical trial in which we give an antibody treatment to patients undergoing CAR T-cell therapy, which may help reduce risk of related neurological toxicity. Our team is also participating in clinical trials investigating allogeneic CAR T cells. With this treatment, patients receive genetically modified CAR T cells from a donor. This method may hasten therapy compared with waiting on the patient’s manufactured immune cells. We are also collaborating with Karmanos experts specializing in solid tumor oncology for clinical trials with CAR T-cell therapy. These trials involve other cellular treatments for breast, lung, prostate, head and neck, and gynecologic cancers.

Karmanos specialists have experience in providing commercially approved and investigational cellular therapies. As a National Cancer Institute–Designated Comprehensive Cancer Center, we work closely with investigators developing novel strategies to make this therapy safer, develop pathways toward new indications, and ensure more accessibility to CAR T-cell therapy. With our robust clinical trials program and experienced team, we are committed to further improving outcomes for patients who are candidates for these therapies and to overcoming challenges associated with them.

REFERENCES
Advances in Site Self-Assessment Tools Aim to Bolster Equity in Clinical Trials

by KYLE DOHERTY

NATIONAL CANCER INSTITUTE

(NCI)-designated comprehensive cancer centers routinely perform clinical trial site self-assessments. These assessments include evaluations of trial portfolios and statuses, enrollment metrics, and patient demographics. However, participation in these types of assessments is far less commonplace among community oncology sites.1,2

To address this unmet need, clinical trial site self-assessment tools have been developed to assist sites evaluate and improve their recruitment processes.

“These tools help you [evaluate] the large categories: structural, clinical, physician, patient policy, [and] leadership, to try and make sure that all of those practices, policies, and procedures are supportive of enrollment of underrepresented minorities,” Carmen E. Guerra, MD, MSCE, FACP said in an interview with OncologyLive®.

Guerra is vice chair of diversity and inclusion in the Department of Medicine, Perelman School of Medicine and founding associate director of diversity and outreach at Abramson Cancer Center, University of Pennsylvania in Philadelphia, Pennsylvania.

HISTORIC TOOLS STILL HOLD VALUE

Patients of racial and ethnic minority groups are less likely to enroll in clinical trials. Despite Black and Hispanic individuals representing 13.4% and 18.5% of patients with cancer, only up to 6% of both groups are enrolled in clinical trials. More than half (55%) of patients, however, will agree to enroll in a trial if they are offered participation, irrespective of their race or ethnicity.1,2

In January 2022, Guerra et al performed a literature review to identify scored evaluation tools that provide objective or subjective benchmarks of cancer clinical trial site fairness. Investigators identified 600 articles and organized nonscored tools and strategies into broad categories.3 They identified 2 primary self-assessment tools for cancer clinical trial sites: the NCI Clinical Trial Assessment of Infrastructure Matrix (CT AIM) and the Society for Clinical Research Sites (SCRS) Diversity Site Assessment Tool (DSAT).3

The CT AIM is an unvalidated questionnaire with 37 items or indicators across 11 attribute classifications including trial characteristics such as physician engagement, education standards, and quality assurance.4 Each attribute contains multiple items that aid sites in evaluating their efficiency in each area. The items are scored from prelevel (lowest rating) to level 3 (highest rating).

Shortcomings of the CT AIM tool include clinical trial portfolio diversity and management, in which indicators are related to trial characteristics, phases, purpose types, and disease types. “[With CT AIM] there is not [much] attention paid to the diversity and inclusion of patients, which is why the SCRS DSAT was proposed in 2020,” Guerra said. “CT AIM is focused on [helping sites] have the infrastructure needed to recruit patients to trials. The [SCRS DSAT] is entirely focused on best practices for recruiting and meeting the needs of more diverse patient populations.”

SCRS DSAT is a validated 25-item questionnaire divided into 3 domains: site overview, site recruitment and outreach, and patient-focused services. Each item prompts the participant to score their site on a 6-point scale with higher scores being an indication of increased use of best practices for recruiting diverse patient populations into clinical trials. Background information is also collected for the participants in a fourth section.3

In 2020, a study was conducted evaluating the reliability and validity of the SCRS DSAT. Approximately 17,000 representatives from SCRS member sites were surveyed. Investigators found that the tool displayed “exceptional reliability.” The Cronbach alpha for internal consistency reliability was 0.929. No statistically significant relationship was observed between site characteristics and their DSAT scores.

The mean score on the site overview section was 51.0 (range, 24-60; SD, 8.14). Mean scores of 43.42 (range, 10-54; SD, 9.36) and 26.83 (range, 10-36; SD, 6.80) were reported for site recruitment/outreach and patient-focused services, respectively. Overall, the mean DSAT score was 121.7 (range, 54-150; SD, 20.7).

The study authors concluded that the DSAT can confidently be used to identify areas of improvement for site best practices. “Both [the CT AIM and the DSAT] have their pluses and minuses,” Guerra said, adding that the appropriate tool depends on the goals of the site. “If you are a new site and you want to understand what it [will] take to perform at the very...
FIGURE 1. Example Questions from ASCO-ACCC EDI Site Self-Assessment Tool\(^7\)

There are 7 domains in which respondents evaluate their institutions on a 5-point scale of strongly disagree to strongly agree.

**Supporting patient retention**
Our site/network routinely analyzes feedback and retention data from patients and implements changes to address any racial and ethnic disparities.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Supporting patient participation**
Our site/network has specific goals and effective strategies that help to increase cancer treatment trial participation.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Offering cancer treatment trials**
Our site/network routinely analyzes data about patients who are offered/referred to a cancer treatment trial and implements changes to address any racial and ethnic disparities in offering/refering patients to trials.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Screening patients for cancer treatment trials**
Our site/network has an accountability system(s) for our patient screening and eligibility assessments to help prevent racial and ethnic disparities.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Availability of cancer treatment trials**
Our site/network has partnerships with other organizations, including other health care organizations and/or research networks, to enable us to refer patients to offsite/network locations when no cancer treatment trial is available at our site/network.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mission and leadership**
Our organization has a policy to screen every patient for cancer treatment trials.

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient access**
Our site/network addresses barriers related to travel that might otherwise affect the ability of individuals to access cancer care and services at our site/network (eg, parking vouchers and access to transportation programs).

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Somewhat disagree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACCC; Association of Community Cancer Centers; ASCO, American Society of Clinical Oncology; EDI, equity, diversity, and inclusion.

best [level] and what those best practices are, CT AIM is a place to start. But as you begin to establish this infrastructure, you might want to think about what it takes to be inclusive and enroll a diverse set of patients, because that is what excellence is being defined as by our sponsors and our accrediting and other external bodies. [In that case,] the DSAT is what you want to [use].”

**INNOVATIONS LEAD TO IMPROVEMENTS**
On July 25, 2022, the American Society of Clinical Oncology (ASCO) and the Association of Community Cancer Centers (ACCC) announced the release of 2 new tools to aid clinical trial sites in addressing racial and ethnic disparities in clinical trials: the Just ASK Increasing Diversity in Cancer Clinical Research: An ACCC-ASCO Training Program and the ASCO-ACCC Equity, Diversity, and Inclusion Research Site Self-Assessment.\(^7\)

The Just ASK Training Program is adapted from a course developed at Duke University in Durham, North Carolina on implicit bias. The program is applicable to all members of the clinical trial site research team and can be completed in approximately 90 minutes. Five interactive modules provide information on structural and systemic racism, the role of implicit bias in clinical trial recruitment, and recommendations for addressing racial and ethnic disparities in clinical trial settings.

The ASCO-ACCC Equity, Diversity, and Inclusion (EDI) site self-assessment tool is being rolled out following a successful pilot study with 75 participating research sites across the United States which was initiated in May 2021. The tool was refined and revised using feedback collected during the testing period.

The EDI site self-assessment tool helps sites perform an internal review of existing practices and policies and offers evidence-based strategies to improve patient diversity in clinical trials. Respondents evaluate their institutions in 7 domains on a 5-point scale ranging from strongly disagree to strongly agree. The domains include the following: supporting patient retention, supporting patient participation, offering cancer treatment trials, screening patients for cancer treatment trials, availability of cancer treatment trials, mission and leadership, and patient access. An annotated reference list of detailed strategies for improvement is available to assist in developing an action plan based on results.

A poster by Pressman et al presented at the 2022 ASCO Annual Meeting showed that there is room for improvement in the systemic collection and types of data needed to diversify trial populations. These findings underscore the need for tools such as the ASCO-ACCC EDI site self-assessment.\(^7\)

To determine the feasibility of the EDI site-self assessment tools, a pilot study was conducted to aggregate data and 62 sites from the academic (61%), hospital/health system (26%), and independent (13%) settings participated. Only 18% of sites that completed the assessment were able to provide initial screening...
data, none of which were able to show that they routinely collected these data. “Most sites in this study did not collect, or routinely collect, data for screening [patients for], offering [participation in], and [approving patients for] clinical trials,” the study authors wrote. “Without these data, sites are unable to evaluate and monitor whether their patients have equitable access to clinical trials or establish strategies to address any inequities.”

Less than half the sites reported eligibility screening (31%), eligibility confirmation (42%), onsite trials offered (18%), or offsite trials offered (6%). All sites had low rates of routinely collecting this data, at 6%, 15%, 5%, and 0%, respectively (Figure 2).

Most sites were able to provide patient consent data (63%) and 39% of those sites routinely collected this information. Study authors noted that as many as 29% of the sites across steps did not systematically collect the requested data, with some sites indicating it would be too burdensome to manually review charts to extract the necessary data.

The ASCO-ACCC EDI Research Site Self-Assessment tool and the Just ASK Training Program are available for free online and ASCO plans to continue to use feedback from the community to continue to revise and enhance the tools. Guerra noted that future studies will evaluate the efficacy of the tools in recruiting traditionally underrepresented minorities as data matures and becomes available.

References

Read more at bit.ly/3zsXZTV.
**Indication**

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

**Select Safety Information**

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

---

CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.

Please see full Important Safety Information on the following pages.
RAISING THE STANDARD FOR SURVIVAL

In combination with trastuzumab + capecitabine
TUKYSA extended overall survival*1

![Graph showing extended survival comparison between TUKYSA and control arm.]

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash1

Important Safety Information

Warnings and Precautions

• **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

• **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 x ULN, 6% had an AST increase >5 x ULN, and 1.5% had a bilirubin increase >3 x ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

• **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock. Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.
Monitor ALT, AST, and bilirubin prior to starting TUKYSA,

Hepatotoxicity:

- Diarrhea:

**Warnings and Precautions**

- Adverse reactions led to treatment discontinuation in 2% of patients who received TUKYSA including sudden death, dehydration, hypotension, acute kidney injury, and death.
- 6% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4.
- TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death.
- Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.
- Diarrhea led to TUKYSA dose reductions in 6% of patients.
- The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.
- In HER2CLIMB, 8% of patients who received TUKYSA had ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%).
- Adverse reactions occurring in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.
- In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.
- The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

**References:**

TUKYSA® (tucatinib) tablets, for oral use

Brief summary of Prescribing Information (PI). See full PI. Rx Only

INDICATIONS AND USAGE
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSEAGE AND ADMINISTRATION

Recommended Dose
The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

- Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact.
- Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact.

Recommended Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors:
- Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Severe Hepatic Impairment:
For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Recommended TUKYSA Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>250 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>200 mg orally twice daily</td>
</tr>
<tr>
<td>Third</td>
<td>150 mg orally twice daily</td>
</tr>
</tbody>
</table>

Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Hepatotoxicity:
Grade 2 bilirubin (>1.5 to 3 × ULN) Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.

Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> ≥ 3 to 10 × ULN)
Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.

Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)
Permanently discontinue TUKYSA.

Other adverse reactions:
ALT or AST ≥ 3 × ULN AND Bilirubin ≥ 2 × ULN Permanently discontinue TUKYSA.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>Grade (%)</td>
<td>Grade (%)</td>
</tr>
<tr>
<td>All</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>3.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>2.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysthesia syndrome</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy and contraception information.

ADVERSE 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.

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)
The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm.

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>Grade (%)</td>
<td>Grade (%)</td>
</tr>
<tr>
<td>All</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>3.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>2.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysthesia syndrome</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>
CYP3A Substrates: Effects of TUKYSA on Other Drugs

CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

USE IN SPECIFIC POPULATIONS

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

<table>
<thead>
<tr>
<th>Investigation</th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59</td>
<td>3.3</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>47</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased AST</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>40</td>
<td>0.8</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>28</td>
<td>2.5</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NG-CTCAE v4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NG-CTCAE v5.0).

2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.

3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.

4. There is no definition for Grade 2 in CTCAE v4.03.

5. Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increased persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

Strong CYP3A Inducers or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inhibitor decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inhibitor.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor.

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates.

where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

Lactation

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information.

Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

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

Geriatric Use: In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diabetes (9%), vomiting (6%), and anemia (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

Renal Impairment: The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CrCl < 30 mL/min estimated by Cockcroft-Gault equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CrCl] 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
CRESTONE Data Signal Positive Start to Managing Rare NRG1 Fusions in Solid Tumors

by MEGAN HOLLASCH

RESULTS OF THE PHASE 2 CRESTONE study (NCT04383210) have demonstrated the tolerable safety profile and efficacy of seribantumab for the treatment adult patients with metastatic solid or locally advanced tumors harboring the rare NRG1 fusions. Initial findings were presented at the 2022 American Society of Clinical Oncology Annual Meeting.

In CRESTONE, the investigator-assessed objective response rate (ORR) with seribantumab for cohort 1 (n = 12) was 33% with 2 partial responses (PR) and 2 complete responses (CR). Of the 12 patients in cohort 1, 11 had non-small cell lung cancer (NSCLC), for whom the ORR was 36% and included 2 PRs and 2 CRs.

NRG1 fusions are found in 0.2% of all solid tumors and the oncolytic drivers associated with overactivation of HER3. Seribantumab, an anti-HER3 monoclonal antibody, demonstrated preclinical activity in NRG1 fusion-driven preclinical models.

Yasir Y. Elamin, MD, an assistant professor in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas said, “The data are an important finding, but we must be conscious that the numbers are limited. This analysis was only done on 12 patients so I would like to see more numbers.”

In an interview with OncologyLive®, Elamin discussed how the early data support further investigation of seribantumab, which is especially important as there are no current approved targeted therapies for patients with NRG1 fusions.

Please describe the background on NRG1 fusions and solid tumors and the practice for detecting these fusions. NRG1 fusions result from the fusion of the NRG1 gene with another partner gene. They are very rare, and the overall [incidence] is 0.2% in all solid tumors, but they are enriched in adenocarcinoma of the lung which is also rare to begin with. It’s also enriched in KRAS wild-type adenocarcinoma of the pancreas.

The NRG1 protein binds to the healthy protein on the surface of the cancer cell, activating downstream signaling, so it does activate the PI3K pathway, the MAPK pathway, and so forth. Given how rare this fusion is, it’s [recently] become a focus of extensive clinical research and preclinical research. What we can tell based on some limited retrospective studies is that patients with NRG1 fusions may not be very responsive to chemotherapy or immunotherapy. Therefore, the treatment options in the metastatic setting are limited.

The best way to test for an NRG1 fusion would be to use an RNA-based sequencing platform because the intronic region in the fused gene is quite large, so it is much easier to detect.

What makes seribantumab unique from other agents in this space? There are [other] pan-ERBB inhibitors, such as tyrosine kinase inhibitors, which would inhibit the entire HER family. One of them that’s already commercially available is afatinib (Gilotrif), although it is not approved specifically for NRG1 fusions.

Seribantumab is a fully humanized monoclonal antibody that binds to HER3 on the cell surface and it essentially competes with NRG1. By doing that, it prevents the diagonalization of HER3 and other HER family members and it will suppress the activation of downstream signaling. Monoclonal antibodies target HER3 and HER2 when they treat [patients with] NRG1-positive tumors.

What inspired the launch of the CRESTONE study? And what are the key objectives of the research? The overall goal of the study is to provide patients with NRG1 fusion-positive tumors with treatment options. We don’t have any FDA-approved targeted drugs for patients with NRG1 fusions and the promise of targeted therapy has been well established across solid tumors. These therapies are typically effective, have fewer adverse events [AEs], and the patients treated with targeted therapy, in most cases, have a better quality of life.

The primary end point of the phase 2 portion of the study is to establish the ORR in 3 different cohorts. The first cohort [includes] patients with NRG1 fusions who were not treated with HER3 targeted therapy or pan-ERBB targeted therapy, and who have their NRG1 fusions centrally confirmed. Then there is a second cohort for patients who have been treated in the past with HER3 targeted therapy or a pan-ERBB inhibitor. And finally, cohort 3 [includes] patients who don’t fit in cohort 1 or cohort 2, and these are mostly patients who lack the EGF-like domain of the NRG1 fusion protein.

What were the efficacy findings reported with this agent? The efficacy that was reported was from cohort 1, which is, again, focused on patients who had no prior ERBB-directed [therapy]. The number of [patients and] what was reported was small, but the data are very encouraging. In this cohort, the efficacy [data included] 12 patients, and 4 of these 12 patients had a response, [for a] response rate of 33%; of these 2 were complete responses and 2 were partial responses. If you look specifically at patients with [which] NSCLC, the overall response rate was 36%. The disease control rate in patients in cohort 1 was 92%.

I think it’s an important finding, but we must be conscious that the numbers are limited. The critical question here is about the efficacy: Is the drug going to be active in all fusion partners? Based on the initial data that we have seen, it [appears] that the fusion partner does not [affect] the efficacy in a negative way.

Generally speaking, the agent was safe and that is evident because we did not see any patients who discontinued service [because of] an AE. The vast majority of AEs were grade 1 or grade 2.

What were the takeaways from this trial? [The data] reinforce the utmost importance of genetic testing, especially in the context of lung cancer. I think it is important to do genetic testing, because it does [affect] clinical decisions, outcomes, and survival. For NRG1 you could miss it if you use the DNA-based [next-generation sequencing]. If you used an RNA-based test, I think that would be the gold standard way of detecting this.

These data that we’ve seen warrant further clinical development of this drug in solid tumors with an NRG1 fusion. We need more targeted therapies for patients; the promise of targeted therapy is real.
Dual Checkpoint Blockade Holds Promise as Long-term Treatment Option in NSCLC

**BIOMARKER SELECTION HAS PLAYED** a crucial role in the rapid advancement of clinical benefit observed for patients with non–small cell lung cancer (NSCLC). At the time of diagnosis of advanced lung cancer molecular testing is imperative and the best marker to have data for is PD-L1, according to Neal E. Ready, MD, PhD.

“We can now identify the right treatment for the right patient [and] I know that there’s a tendency to want to have one-size-fits-all treatment,” Ready said during a recent OncLive® Seminar Series.

“For [patients with] PD-L1-low expressing tumors, we have a certain set of possible treatments [and] for PD-L1-high expressing tumors [there are] different options including monotherapy and other approaches.”

Immunotherapy treatment options for patients with NSCLC with PD-1 or PD-L1 inhibitors have demonstrated durable responses with longer-term follow-up. In addition to monotherapy, chemoimmunotherapy treatment options have expanded the armamentarium for these patients. “We have a lot of different options depending on histology and, presumably, more to come,” said Steven V. Liu, MD, who joined Ready in the seminar.

“The other category we have is dual checkpoint blockade [using] 2 different checkpoint inhibitors: one targeting PD-1 and the other targeting CTLA-4. Both play an important role in priming immune cells,” Liu continued.

CheckMate 227 (NCT02477826) and CheckMate 9LA (NCT03215706) evaluated the immunotherapy combination of nivolumab (Opdivo), a PD-1 inhibitor, and ipilimumab (Yervoy), a CTLA-4 inhibitor, for patients with treatment-naive NSCLC.**1,4**

Updated findings for both trials, 5- and 3-year data, respectively, were presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting (TABLES 1 and 2).**1,2**

During the seminar, Ready and Liu discussed the new data and provided commentary on treatment considerations for patients who are eligible to receive these regimens.

**TREATMENT OPTIONS**

**STEVEN V. LIU, MD:** The combination of nivolumab and ipilimumab has [been shown] to be very effective in melanoma [and] some early success was observed in lung cancer including small cell lung cancer. CheckMate 227 was a bit of a complicated study. It was for patients with advanced NSCLC who had no prior therapy and excluded [patients with] *EGFR* and *ALK* mutations. Patients with squamous and nonsquamous histologies were stratified and this split up [the trial] into almost 2 different studies.

If a patient had PD-L1 expression of 1% or greater they were randomly assigned to nivolumab and ipilimumab plus standard chemotherapy or nivolumab alone, whereas if they had PD-L1-negative disease [they were randomly assigned to one of] 3 arms; nivolumab/ipilimumab, chemotherapy alone, or a third arm that was nivolumab with chemotherapy. The thought here was that giving nivolumab alone to [a patient with] PD-L1-negative disease was not well advised.

The primary end point was observed in data from the PD-L1-positive subgroup and that’s going to have important implications in how we interpret [these data] and maybe, more importantly, how the regimen was approved. Dr Ready, you were involved in the early studies. [Please discuss the] decision to focus on the PD-L1-positive group.

**NEAL READY, MD, PHD:** In the phase 1 trial [CheckMate 012; NCT01454102] we established that the full dose of nivolumab and ipilimumab 1 mg/kg was safe in patients with lung cancer. Because it was a phase 1 trial, we included patients with actionable alterations. Among the 77 patients who had a biomarker analysis for PD-L1, we looked at activity. There were 12 patients with *EGFR* mutations, [which] is a big number.

Usually [*EGFR-mutant*] tumors are low [expressors] for PD-L1, so I think we interpreted that [incorrectly,] that it was [only] the PD-L1-positive patients who were benefiting. That, I think, misled the plan of the trial around the primary end point and, in retrospect, I’m not surprised at all that it looks like the PD-L1-negative subgroup is the one that might benefit the most.
LIU: That’s an interesting point, we should just be excluding the driver-positive lung cancers. CheckMate 227 was a positive study, and this is an FDA-approved regimen [for which] we have long-term follow-up.

These data were presented at ASCO 2022 by Julie R. Brahmer, MD, MSc, [and] are the 5-year results. What we saw here is that the clear winner was dual checkpoint blockade outperforming nivolumab alone and outperforming chemotherapy alone. Those weren’t directly compared but nivolumab and ipilimumab were superior to chemotherapy with a hazard ratio for survival of 0.77.

The impressive piece here is long-term survival. We see it at 3 years: the 3-year rate of survival was 33% vs 22% with chemotherapy; the 4-year survival rate was 28% vs 18%; and the 5-year survival rate was 24% vs 14%. There’s not a whole lot of difference between the 3-year survival and 5-year survival [outcomes]. We really do see that flattening out [of the curve] and remember, there’s no chemotherapy involved in this. We have 1 of 4 patients still alive at 5 years in the PD-L1-positive group.

In the PD-L1-negative group, which was not the primary end point, we see significant benefit. In fact, the hazard ratios here were even better—0.65 for nivolumab/ipilimumab vs chemotherapy. One in 5 patients with PD-L1-negative disease [was] alive at 5 years [with nivolumab/ipilimumab]; however, the FDA approval does not include PD-L1-negative disease as part of the label. I agree that is perhaps where we see a bigger need, maybe even more benefit, with this.

READY: One important part of the PD-L1-negative design in CheckMate 227 is that, unlike a lot of the current trials where chemotherapy is the comparator, it’s not a standard of care anymore. Here, in the PD-L1-negative group we have a comparator arm of nivolumab plus chemotherapy, so we actually have in 1 trial a direct comparison of nivolumab/ipilimumab vs nivolumab/chemotherapy and we see an approximate 10% difference in survival at 3 years, 4 years, and 5 years...I think [those are] significant data that we don’t get in any of the other trials.

LIU: That’s a great point. It’s helpful to see these curves and how the [regimens] perform concurrently. When we look at 5-year survivors, the important point here is that among patients who are alive at 5 years with nivolumab/ipilimumab, the median PFS [progression-free survival] was 5 years. I would interpret this as saying the patients who are alive at 5 years in the nivolumab/ipilimumab arm never progressed.

Individuals in the chemotherapy arm who are alive at 5 years progressed within 9 months in the PD-L1-positive group and went on to some other type of immunotherapy. It’s really showing that it is the immunotherapy that’s driving things, [and] what we’re seeing now in our long-term survivors are steadily increasing numbers of treatment-free intervals where patients are alive and off therapy for 1, 2, or 3 years and climbing. That’s what we want—individuals who are alive and no longer needing any therapy. At some point we’re going to call that a cure.

Another option we have, although it is emerging, is looking at dual checkpoint blockade with chemotherapy. That’s the CheckMate 9LA regimen—nivolumab and ipilimumab long-term with chemotherapy. The difference here is the chemotherapy is only given for 2 cycles, so a very abbreviated course of chemotherapy, and this may be the best of both worlds. You’re getting that initial bump in response rate and PFS where the chemotherapy maybe gives you a little reassurance for individuals who have symptomatic or high-burden disease, but you don’t continue that chemotherapy.

Dr Ready, I don’t know how it is at Duke, but I know at Georgetown, my melanoma colleagues are not believers in the chemotherapy aspect. They think it’s going to prevent memory T-cell formation and they are colored by the biochemistry experience in melanoma where adding chemotherapy to IL-2 did not do anything.¹

Lung cancer is a different disease, and we know from the [findings of other] studies that chemotherapy can play a role, especially in that

---

**TABLE 1. Long-term Efficacy Outcomes in CheckMate 227**¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PD-L1 ≥ 1%</th>
<th>PD-L1 &lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab plus ipilimumab (n = 396)</td>
<td>Chemotherapy (n = 397)</td>
</tr>
<tr>
<td></td>
<td>Nivolumab (n = 396)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (n = 397)</td>
<td></td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>17.1</td>
<td>15.7</td>
</tr>
<tr>
<td><strong>HR vs chemotherapy</strong> (95% CI)</td>
<td>0.77 (0.66-0.91)</td>
<td>0.92 (0.79-1.07)</td>
</tr>
<tr>
<td><strong>36-month OS rate</strong></td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>48-month OS rate</strong></td>
<td>28%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>60-month OS rate</strong></td>
<td>22%</td>
<td>18%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PD-L1 &lt; 1%</th>
<th>PD-L1 &lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab plus ipilimumab (n = 187)</td>
<td>Chemotherapy (n = 186)</td>
</tr>
<tr>
<td></td>
<td>Nivolumab (n = 177)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (n = 186)</td>
<td></td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>17.4</td>
<td>15.2</td>
</tr>
<tr>
<td><strong>HR vs chemotherapy</strong> (95% CI)</td>
<td>0.65 (0.52-0.81)</td>
<td>0.80 (0.64-1.00)</td>
</tr>
<tr>
<td><strong>36-month OS rate</strong></td>
<td>33%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>48-month OS rate</strong></td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>60-month OS rate</strong></td>
<td>19%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**5-year survivors**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PD-L1 ≥ 1%</th>
<th>PD-L1 &lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab plus ipilimumab (n = 80)</td>
<td>Chemotherapy (n = 50)</td>
</tr>
<tr>
<td></td>
<td>Nivolumab (n = 33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (n = 12)</td>
<td></td>
</tr>
<tr>
<td><strong>Median PFS, months</strong> (95% CI)</td>
<td>59.1 (35.8-NA)</td>
<td>9.3 (7.0-22.1)</td>
</tr>
<tr>
<td><strong>5-year PFS rate</strong> (95% CI)</td>
<td>49% (37%-60%)</td>
<td>14% (4%-28%)</td>
</tr>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>80% (69.9%-87.6%)</td>
<td>54% (39.3%-68.2%)</td>
</tr>
<tr>
<td><strong>Median DOR, months</strong> (95% CI)</td>
<td>NR (52.6-NA)</td>
<td>12.4 (5.6-24.4)</td>
</tr>
<tr>
<td><strong>5-year DOR (95% CI)</strong></td>
<td>54 (40-66)</td>
<td>17 (6-36)</td>
</tr>
</tbody>
</table>

**Treatment-free discontinuation of study therapy** (95% CI)

<table>
<thead>
<tr>
<th>Duration</th>
<th>PD-L1 ≥ 1%</th>
<th>PD-L1 &lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 12 months</td>
<td>74% (63.7-82.0)</td>
<td>29% (17.2-42.3)</td>
</tr>
<tr>
<td>≥ 24 months</td>
<td>67% (56.6-76.1)</td>
<td>23% (12.3-35.5)</td>
</tr>
<tr>
<td>≥ 36 months</td>
<td>66% (55.5%-75.1%)</td>
<td>20% (10.0%-32.7%)</td>
</tr>
</tbody>
</table>
PD-L1-negative group. This strategy allows us to avoid the chemotherapy long term and what we saw was a clear survival benefit in favor of the nivolumab/ipilimumab/chemotherapy arm. The limited course of chemotherapy had an OS [overall survival] benefit with a hazard ratio of 0.74. In the 3-year update also presented at 2022 ASCO by Luis Paz-Ares, MD, PhD, we saw an improvement in PFS with a hazard ratio of 0.7 and an improvement in response rate increasing from 25% to 38%.

We get that initial benefit of the chemotherapy and that long-term survival benefit with nivolumab/ipilimumab. When we look at the PD-L1-positive group we see a hazard ratio of 0.74 favoring the nivolumab/ipilimumab combination. In the PD-L1-negative group there was a hazard ratio of 0.67 favoring that nivolumab/ipilimumab combination. It’s another chemotherapy-immunotherapy combination but bridges those therapies.

We’re using dual checkpoint blockade in the maintenance setting but not really continuing that long-term chemotherapy. Dr Ready, I don’t know if this is a regimen that has found its way into your practice at all.

**READY:** Yes, for patients with low PD-L1 scores and [who] I think...have neoantigens, are smokers, have high tumor mutational burden, or other factors [for which] I would be afraid to not give chemotherapy. That’s the type of scenario where I would use the CheckMate 9LA regimen.

**LIU:** We have a lot of different options and need to tailor them. When I think of dual checkpoint blockade there are different toxicities. Dr Ready, what adverse effects do you notice more in patients receiving dual checkpoint blockade? If we’re looking at adding CTLA-4, does that add any kind of toxicity dimension?

**READY:** I think of colitis and pituitary inflammation with ipilimumab. I think of those coupled but then some other rare ones will just rear up when you add ipilimumab.

**LIU:** If you give enough immunotherapy, you start seeing rare adverse effects periodically and the key is recognition and a high degree of vigilance so we can intervene early. Colitis is something that we did see at very high rates with ipilimumab in the early studies.

We were still figuring out the dose and Dr Ready I know that you were involved in some of those dose-finding studies. There is a difference in the dosing for [ipilimumab] in lung cancer compared with melanoma, right?

**READY:** Yes, in the CheckMate 012 trial we specifically tried the melanoma regimen in lung cancer [and] we proved that you cannot use the same [administration]. We systematically studied the ipilimumab dose to the point where we felt that we had the sweet spot between giving enough to stimulate the immune system but keeping it at a tolerable level.

**LIU:** I agree. It is important for those of us who treat multiple diseases [to remember] the different doses. I know it seems counterintuitive but to me it makes a lot of sense because the immune system that allows melanoma to escape is very different from an immune system that allows melanoma to escape.


**PD-L1 < 1%**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab plus ipilimumab plus chemotherapy (n = 135)</th>
<th>Chemotherapy (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>17.7</td>
<td>9.8</td>
</tr>
<tr>
<td>ORR (95%CI)</td>
<td>0.67 (0.51-0.88)</td>
<td></td>
</tr>
</tbody>
</table>

**PD-L1 ≥ 50%**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab plus ipilimumab plus chemotherapy (n = 76)</th>
<th>Chemotherapy (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>18.9</td>
<td>12.9</td>
</tr>
<tr>
<td>ORR (95%CI)</td>
<td>0.75 (0.53-1.07)</td>
<td></td>
</tr>
</tbody>
</table>

DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

**REFERENCES**


Young-Onset Diagnoses Continue to Rise in Pancreatic and Biliary Cancers

by Ryan Scott

Although rates of patients diagnosed with pancreatic cancer and biliary cancer continue to rise, a disproportionate increase has been seen in younger patients. Investigators postulate that this increased incidence may be because of lifestyle changes including lack of access to healthy food, obesity, and increased use of antibiotics, all of which can influence the gut microbiome, according to Alok Khorana, MD.

Data from a retrospective cohort study of 360,764 patients who received a diagnosis of pancreatic or biliary cancer between 2004 and 2017 showed that the number of patients with young-onset pancreatic or biliary cancer increased by 33.3% during the study period, and the risk for stage IV disease (6.4% of all patients) was higher than that of stage I-III disease (5.4% of all patients; odds ratio, 1.25; 95% CI, 1.21-1.29).

“We need to drill down more into understanding risk factors, and the fact that many of these patients presented at a more advanced stage is troubling,” Khorana said. “At this point, we still need to figure out what etiologic factors are driving this. In colorectal cancer [CRC], we’ve shown that the gut microbiome—the microorganisms that line the gastrointestinal tract—may be different in younger patients vs older patients, and we’re working to see if that’s also the case in pancreas and biliary cancers.”

In an interview with OncologyLive®, Khorana, a professor of medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, the Sondra and Stephen Hardis Chair in Oncology Research, the vice-chair for Clinical Services of the Taussig Cancer Institute, and the director of the Gastrointestinal Malignancies Program at the Cleveland Clinic in Ohio, discussed on-the-rise pancreatic and biliary cancer rates in younger patients, plus the rationale of potential future research into the role of the gut microbiome in these patients.

Q: What were the key takeaways from this research?

This was primarily a retrospective cohort study. We took data from the National Cancer database and analyzed it over a set period in the past decade. We examined rates of young-onset pancreas and biliary cancer by year, following trends. In general, pancreas and biliary cancers have increased, but the increase was [evident] in the younger population.

Unfortunately, that’s what we are seeing in our clinic these days. We see people who are in their 40s or mid 30s with a new diagnosis of pancreas and biliary cancer. This is a topic that deserves more attention.

We identified a 33% increase in the rate of young-onset pancreatic cancer and biliary cancer. This is in the context of a large increase in the incidence of pancreas and biliary cancers regardless of age. But the fact that rates are increasing in younger patients is troubling.

We don’t fully understand why. We did find that patients who are minorities, such as African American patients or Hispanic patients, had a disproportionately higher rate of increased incidence, but the majority of patients with young-onset pancreatic or biliary cancer are primarily White. Although the increased rates appear in patients who are African American or Hispanic, it’s still present across all races. We need to understand why that’s happening.

Q: You mentioned some underrepresented populations have a higher likelihood of receiving a pancreatic or biliary cancer diagnosis. Why might this be?

We don’t quite know. It may be driven by gut microbiome, which is important for other types of young-onset cancers. It may be driven by lack of access to healthier food, fresh produce, and more balanced diets. For example, obesity rates are higher in some of these [underrepresented] populations. It may be related to obesity, lack of exercise, or more exposure to smoking and alcohol. We don’t fully understand these findings, but that’s what we need to work on to try to better figure out.

Q: Why do you believe that we are seeing younger patients with cancers typically associated with older patients?

In general, there’s been a big change in lifestyle for all people over the past several decades. We see, especially in children that were born in the 1970s, 1980s, and 1990s, that there has been an increasing use of antibiotics in younger children and more obesity in younger people. There’s a lack of access to balanced diets among younger people. All these factors can influence the gut microbiome.

We think that’s how this is playing out, and as more emphasis is placed on plant-based diets, we hope that these trends will change. But for right now, every year that we examined had an increase in incidence in younger patients with pancreatic cancer. It is a worrisome trend, and we need to drill down further into why this is happening.

Q: Could you expand on the importance of studying the gut microbiome in patients?

Microbiomics is the science of trying to understand the microorganisms that live in our body. We think of a body as ours but it’s actually made up of millions of microorganisms that happily live with us. They are good for us in terms of helping digest foods but also may alter our brain function, alter our gut function, and even reduce or increase our risk of cancer. This is a science that’s only been developed in the past decade or so.

The findings suggest that alterations in the gut microbiome can sometimes be bad for people in terms of increasing the risk of cancer. But that does not mean that there’s a certain microorganism that’s bad. Rather, patients could have a microbiome profile that correlates with cancer. The biggest question is if we eat a better diet, have a better lifestyle, strive toward healthier living, and make these changes, will the microbiome profile revert to [lowering the risk] of cancer? Will that affect these increased young cancers that we’re seeing?

Q: Why is it important to evaluate younger patients for these cancers?

Physicians should be much more aware of the possibility that younger people can develop cancers that we previously thought were for older people only. This can include CRC, pancreas cancer, or bladder cancer. All these cancers can occur in 30-, 40-, and 50-year-olds.

Sadly, many patients are turned away by their physicians because their symptoms are ascribed to something else, such as irritable bowel syndrome or inflammatory bowel disease, and they are not fully investigated because cancer is very low in the differential diagnosis.

That may have been accurate a couple decades ago, but in this era, where we’re seeing this increasing emphasis on young-onset cancers, it’s important to ensure that younger people are evaluated for cancer, just as they would be if they were older.
THE FUTURE OF TREATMENT in TP53-mutated mantle cell lymphoma (MCL) depends on further research to find more effective therapies for this patient subset, according to Tycel Jovelle Phillips, MD.

For instance, in the phase 3 SHINE trial (NCT01776840), ibrutinib (Imbruvica) in combination with bendamustine plus rituximab (Rituxan; BR) demonstrated a 17.8-month progression-free survival (PFS) benefit over placebo plus BR in this population, with a median PFS of 28.8 months with ibrutinib vs 11.0 months with placebo, Phillips explained in a presentation at the 2022 Pan Pacific Lymphoma Conference. Although investigators observed a PFS benefit, it was lower than the median PFS of 80.6 months for the entire studied population of patients with MCL.

“Right now, the big question is how to best treat these patients and how to best continue to keep them alive,” Phillips said. “More studies are needed with new novel combinations, and we’ll need more new drugs to enter the market that are hopefully agnostic to TP53 mutations.”

In an interview with OncologyLive, Phillips, a clinical associate professor in the Division of Hematology and Oncology at The University of Michigan Rogel Cancer Center in Ann Arbor, outlined the reasons why TP53 mutations are difficult to treat and discussed potential future directions for the treatment of this subgroup of MCL.

What are some of the unanswered questions regarding TP53 mutations in MCL?

One question regarding the role of TP53 mutations is: Should they affect how we treat patients with MCL? The mutation itself is rare, appearing in about 20% of patients, but it seems to have poor prognostic effects on outcome and treatment response. If we look at all the information we have to date about up-front therapy and salvage therapy, patients who harbor this mutation tend to have worse outcomes than those who don’t. [Additionally, this mutation doesn’t] seem to have any clear treatment modality; it seems to be agnostic to treatments other than potentially [chimeric antigen receptor] CAR T-cell therapy.

As a background, TP53 is our master tumor suppressor. Patients can have either TP53 deletion through loss of chromosome 17p, or mutations in the p53 protein. It does appear that the mutation tends to be a bit more detrimental to a patient’s outcome than the deletion, because there are 2 copies of the gene, so if a patient loses 1 copy [through deletion], there’s always the possibility that they have another intact copy. Patients can have monoallelic or biallelic deletions. However, the [TP53] mutation is a dominant negative, so if a patient has a mutated copy, it affects and inactivates the normal copy, and they lose all complete function in [TP53].

What potential therapies are still needed to increase the benefit of treatment in patients with p53-mutated disease?

These are probably our highest-risk patients. Identifying a treatment regimen that can give a durable remission [would be ideal]. MCL is incurable, so we’re not curing any of these patients. However, the end goal in this disease is to prolong the remission as long as possible. We need to come up with new induction therapies that will provide remissions in most of these patients beyond 24 months, and then move on to better salvage therapies to continue to extend the OS of these patients.

What ongoing studies within this patient population would you like to highlight?

A [phase 2] trial [NCT03824483] at Memorial Sloan Kettering Cancer Center is looking at a combination of obinutuzumab [Gazyva], venetoclax [Venclexta], and zanubrutinib [Brukinsa], which is a second-generation [Bruton tyrosine kinase] BTK inhibitor. That trial is immature, as we still don’t have the 24-month readout on the patients who received that induction therapy.

Other than that, unfortunately, most studies that have been published have not shown effective results, at least in the up-front setting for these patients with TP53-mutated disease. A study that was done in the Netherlands that looked at combining ibrutinib and lenalidomide [Revlimid] in this patient population seemed to have a decent outcome. [However, that is not reflective of] the way the field is going as far as combining these 2 agents in the relapsed/refractory setting.

Another direction may be combining BTK inhibitors with the BCL2 inhibitor venetoclax, although most of the studies so far with a BCL2 inhibitor plus a BTK inhibitor haven’t demonstrated any substantial impact in TP53-mutated cases.

What main message from your presentation would you like colleagues to walk away with?

We need better studies, whether that’s by moving CAR T-cell therapy into the frontline setting or using the wave of bispecific antibodies that are entering the field. We’ll need to wait to see how future studies read out to determine whether these therapies will move up to the up-front setting and be useful for these patients.

[The situation with these patients with TP53 mutations is] unfortunate because we’ve come so far with MCL. [In MCL as a whole,] we’ve improved survival quite a bit, and most of these patients can expect to live a decade or longer. We need to play catch-up with this high-risk group. We can identify these patients, now we just need to find the best way to treat them.
Now Approved.

A treatment designed for your cytopenic myelofibrosis patients.¹

To learn more, visit VONJO.com

Indication
VONJO™ (pacritinib) is indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]) myelofibrosis (MF) with a platelet count below $50 \times 10^9/L$.

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

VONJO is available as 100 mg capsules, for oral use.

Important Safety Information

CONTRAINDICATIONS
VONJO is contraindicated in patients concomitantly using strong CYP3A4 inhibitors or inducers as these medications can significantly alter exposure to pacritinib, which may increase the risk of adverse reactions or impair efficacy.

Please see Important Safety Information and Brief Summary on the following pages and full Prescribing Information at VONJO.com.

VONJO™ is a trademark of CTI BioPharma Corp. ©2022 CTI BioPharma Corp. All rights reserved. US-PAC-2100040 03/2022
Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Risk of Infection: Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting therapy with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

DRUG INTERACTIONS

Effect of Other Drugs on VONJO: VONJO is predominantly metabolized by CYP3A4. Coadministration of VONJO with strong CYP3A4 inhibitors or inducers are contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

Effect of VONJO on Other Drugs: VONJO is an inhibitor of CYP1A2, CYP3A4, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter 1 (OCT1) in vitro. Concomitant administration of VONJO with these substrates may increase their plasma concentrations. Avoid coadministration of VONJO with drugs that are sensitive substrates of CYP1A2, CYP3A4, P-gp, BCRP, or OCT1.

ADVERSE REACTIONS

Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with best available therapy (BAT). The fatal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningoencephalitis, and acute myeloid leukemia in <1% of patients each, respectively.

Serious adverse reactions occurred in 47% of patients treated with VONJO 200 mg twice daily and in 31% of patients treated with BAT. The most frequent serious adverse reactions occurring in ≥3% patients receiving VONJO 200 mg twice daily were anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%), and squamous cell carcinoma of skin (3%).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients receiving VONJO 200 mg twice daily compared to 12% of patients treated with BAT. The most frequent reasons for permanent discontinuation in ≥2% of patients receiving VONJO 200 mg twice daily included anemia (3%) and thrombocytopenia (2%).

The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, nausea and vomiting, rash, and fatigue. The most frequently reported events (greater than or equal to 1%) include diarrhea (47%), nausea (35%), vomiting (30%), rash (26%), fatigue (25%), and anemia (23%).

Diabetes mellitus, hyperglycemia, and hyperuricemia were also reported at an incidence of at least 5% in patients treated with VONJO 200 mg twice daily.

Use of VONJO is associated with an increased risk of bleeding events, including gastrointestinal, renal, and cutaneous. The incidence of serious bleeding events was higher in VONJO-treated patients than in patients treated with BAT (3.6% vs 2.3%). The most common serious bleeding events in VONJO-treated patients included intracranial hemorrhage, gastrointestinal hemorrhage, and multiorgan failure, cerebral hemorrhage, meningoencephalitis, and acute myeloid leukemia in <1% of patients each, respectively.

The most frequently reported serious bleeding events (events with an incidence of at least 1%) include gastrointestinal hemorrhage (2.8%), cerebral hemorrhage (1.4%), intracranial hemorrhage (1.4%), and multiorgan failure (1.0%).

WARNINGS AND PRECAUTIONS

Hemorrhage: Serious (1%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <100 x 10^9/L. Serious (13%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <50 x 10^9/L. Grade ≥3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively. Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures.

Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention. In the case of severe bleeding, hold VONJO until hemorrhage resolves. When the bleeding has resolved, restart treatment at 50% of the last given dose. If the bleeding recurs, discontinue treatment with VONJO. In the event of life-threatening bleeding, discontinue VONJO.

Diarrhea: VONJO caused diarrhea in approximately 48% of patients compared to 15% of patients treated with the control arm. The median time to resolution in VONJO-treated patients was 2 weeks. The incidence of reported diarrhea decreased over time with only 41% of patients reporting diarrhea in the first 8 weeks of treatment, 15% in Weeks 8-16, and 8% in Weeks 16-24. Diarrhea resulted in treatment interruption in 3% of VONJO-treated patients. None of the VONJO-treated patients reported diarrhea that resulted in treatment discontinuation. Serious diarrhea adverse reactions occurred in 2% of patients treated with VONJO compared to none in the control arm.

Control preexisting diarrhea before starting VONJO treatment. Manage diarrhea with antidiarrheal medications, fluid replacement, and dose modification. Treat diarrhea with antidiarrheal medications promptly at the first onset of symptoms. Intermittent or reduce VONJO dose in patients with significant diarrhea despite optimal supportive care. In patients with Grade 3 or 4 diarrhea, hold VONJO until it resolves to Grade ≤1 or baseline, and restart VONJO at the last given dose. Intensively antidiarrheal regimen and provide fluid replacement. For recurrent diarrhea, hold VONJO until the diarrhea resolves to Grade ≤1 or baseline, and restart VONJO at 50% of the last given dose once the toxicity has resolved. Concomitant antidiarrheal treatment is required for patients restarting VONJO.

Thrombocytopenia: VONJO can cause thrombocytopenia. VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting moderate to severe thrombocytopenia (platelet count <100 x 10^9/L). VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting severe thrombocytopenia (platelet count <50 x 10^9/L). Monitor platelet count prior to VONJO treatment and as clinically indicated during treatment. Intermittent VONJO in patients with clinically significant worsening of thrombocytopenia that lasts for more than 7 days. Restart VONJO at 50% of the last given dose once the toxicity has resolved. If toxicity recurs, hold VONJO. Restart VONJO at 50% of the last given dose once the toxicity has resolved.

Prolonged QTc Interval: VONJO can cause prolongation of the QTc interval. QTc prolongation of >500 msec was higher in VONJO-treated patients than in patients in the control arm (1.4% vs 1%). QTc increase from baseline by 60 msec or higher was greater in VONJO-treated patients than in control arm patients (1.9% vs 1%). Adverse reactions of QTc prolongation were reported for 3.8% of VONJO-treated patients and 2% of control arm patients. No cases of torsades de pointes were reported.

Avoid use of VONJO in patients with a baseline QTc of >480 msec. Avoid use of drugs with significant potential for QTc prolongation in combination with VONJO. Correct hypokalemia prior to and during VONJO treatment. Manage QTc prolongation using VONJO interruption and electrolyte supplementation. In the case of QTc prolongation >500 msec or >80 msec from baseline, hold VONJO. If QTc prolongation resolves to ≤480 msec or baseline within 1 week, restart VONJO at the same dose. If time to resolution is >1 week, restart VONJO at a reduced dose.

Major Adverse Cardiac Events (MACE): Another JAK inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis: Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies: Another JAK inhibitor has increased the risk of lymphoma and other malignancies, excluding non-melanoma skin cancer (NMSC), (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients who are current or past smokers are at additional increased risk.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no available data on VONJO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. Consider the benefits and risks of VONJO for the mother and possible risks to the fetus when prescribing VONJO to a pregnant woman.

Lactation: There are no data on the presence of pacritinib in either human or animal milk, the effects on the breastfed child, or the effects on milk production. It is not known whether VONJO is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with VONJO, and for 2 weeks after the last dose.

Infertility: Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib may impair male fertility in humans.

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

Hepatic Impairment: Administration of a single dose of VONJO 400 mg to subjects with hepatic impairment resulted in a decrease in the geometric mean area under the concentration curve (AUC) of pacritinib by 8.5%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C], respectively, compared to subjects with normal hepatic function. Avoid use of VONJO in patients with moderate [Child-Pugh B] or severe hepatic impairment [Child-Pugh C].

Renal Impairment: Administration of a single dose of VONJO 400 mg to subjects with renal impairment resulted in approximately 30% increase in maximal concentration (C_{max}) and AUC of pacritinib in subjects with eGFR 15 to 29 mL/min and eGFR <15 mL/min on hemodialysis compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use of VONJO in patients with eGFR <30 mL/min.

Please see Brief Summary on the following pages and full Prescribing Information at VONJO.com.

US-PAC-2000045 02/2022
VONJO™ (pacritinib) capsules, for oral use

Initial U.S. Approval: 2022

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

1 INDICATIONS AND USAGE
VONJO™ (pacritinib) is indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocytosis [PET]) myelofibrosis (MF) with a platelet count below 50 x 10^9/L.

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

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage of VONJO is 200 mg orally twice daily, with or without food. Swallow capsules whole. Do not open, break, or chew capsules.

Patients who are on treatment with other kinase inhibitors before the initiation of VONJO must taper or discontinue according to the prescribing information for that drug.

4 CONTRAINDICATIONS
VONJO is contraindicated in patients concomitantly using strong CYP3A4 inhibitors or inducers as these medications can significantly alter exposure to pacritinib, which may increase the risk of adverse reactions or impair efficacy.

5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Serious (11%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <100 x 10^9/L. Serious (13%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <50 x 10^9/L. Grade ≥3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively.

Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures. Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention.

5.2 Diarrhea
VONJO caused diarrhea in approximately 48% of patients compared to 15% of patients treated with the control arm. The median time to resolution in VONJO-treated patients was 2 weeks. The incidence of reported diarrhea decreased over time with 41% of patients reporting diarrhea in the first 8 weeks of treatment, 15% in Weeks 8-16, and 8% in Weeks 16-24. Diarrhea resulted in treatment interruption in 3% of VONJO-treated patients. None of the VONJO-treated patients reported diarrhea that resulted in treatment discontinuation. Serious diarrhea adverse reactions occurred in 2% of patients treated with VONJO compared to no such adverse reactions in patients in the control arm.

Control preexisting diarrhea before starting VONJO treatment. Manage diarrhea with anti-diarrheal medications, fluid replacement, and dose modification. Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms. Interrupt or reduce VONJO dose in patients with significant diarrhea despite optimal supportive care.

5.3 Thrombocytopenia
VONJO can cause worsening thrombocytopenia. VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting moderate to severe thrombocytopenia (platelet count <100 x 10^9/L). VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting severe thrombocytopenia (platelet count <50 x 10^9/L). Monitor platelet count prior to VONJO treatment and as clinically indicated during treatment. Interrupt VONJO in patients with clinically significant worsening of thrombocytopenia that lasts for more than 7 days. Restart VONJO at 50% of the last given dose once the toxicity has resolved. If toxicity recurs, hold VONJO. Restart VONJO at 50% of the last given dose once the toxicity has resolved.

5.4 Prolonged QT Interval
VONJO can cause prolongation of the QTc interval. QTc prolongation of >500 msec was higher in VONJO-treated patients than in patients in the control arm (1.4% vs 1%). QTc increase from baseline by 60 msec or higher was greater in VONJO-treated patients than in control arm patients (1.9% vs 1%). Adverse reactions of QTc prolongation were reported for 3.8% of VONJO-treated patients and 2% of control arm patients. No cases of torsades de pointes were reported.

Avoid use of VONJO in patients with a baseline QTc of >480 msec. Avoid use of drugs with significant potential for QTc prolongation in combination with VONJO. Correct hypokalemia prior to and during VONJO treatment. Manage QTc prolongation using VONJO interruption and electrolyte management.

5.5 Major Adverse Cardiac Events (MACE)
Another Janus associated kinase (JAK) inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

5.6 Thrombosis
Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

5.7 Secondary Malignancies
Another JAK inhibitor has increased the risk of lymphoma and other malignancies, excluding non-melanoma skin cancer (NMSC), (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

5.8 Risk of Infection
Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting therapy with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

5.9 Interactions With CYP3A4 Inhibitors or Inducers
Coadministration of VONJO with strong CYP3A4 inhibitors or inducers is contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

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

- Hemorrhage [see Warnings and Precautions (5.1)]
- Diarrhea [see Warnings and Precautions (5.2)]
- Thrombocytopenia [see Warnings and Precautions (5.3)]
- Prolonged QT Interval [see Warnings and Precautions (5.4)]
- Major Adverse Cardiac Events [see Warnings and Precautions (5.5)]
- Thrombosis [see Warnings and Precautions (5.6)]
- Secondary Malignancies [see Warnings and Precautions (5.7)]
- Risk of Infection [see Warnings and Precautions (5.8)]

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
6 ADVERSE REACTIONS (cont.)
6.1 Clinical Trials Experience (cont.)

PERSIST-2 Trial

The safety of VONJO was evaluated in the randomized, controlled PERSIST-2 trial. In PERSIST-2, key eligibility criteria included adults with intermediate or high-risk primary or secondary (PPV or PET) MF with spleenomegaly and a platelet count ≤100 × 10^9/L. Prior JAK inhibitor therapy was permitted. Patients received VONJO at 200 mg twice daily (n=106), 400 mg once daily (n=104), or best available therapy (BAT) n=98. Forty-seven (44%) of the 106 patients treated with VONJO 200 mg twice daily had a baseline platelet count of <50 × 10^9/L. The 400 mg once daily dose could not be established to be safe, so further information on this arm is not provided.

In PERSIST-2, among the 106 patients treated with VONJO 200 mg twice daily, the median baseline hemoglobin was 9.7 g/dL, and the median drug exposure was 25 weeks. Fifty-four percent of patients were exposed for 6 months, and 18% were exposed for approximately 12 months. Accounting for dose reductions, the average daily dose (mean relative dose intensity) and median daily dose (median relative dose intensity) were 380 mg (95%) and 400 mg (100%), respectively, for patients receiving VONJO twice daily.

The median age of patients who received VONJO 200 mg twice daily was 67 years (range: 39 to 85 years), 59% were male, 86% were White, 3% were Asian, 2% were Native Hawaiian or Other Pacific Islander, 0% were Black, 9% did not report race, and 87% had an Eastern Cooperative Oncology Group performance status of 0 to 1.

Serious adverse reactions occurred in 47% of patients treated with VONJO 200 mg twice daily and in 31% of patients treated with BAT. The most frequent serious adverse reactions occurring in ≥3% patients receiving VONJO 200 mg twice daily were anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%), and squamous cell carcinoma of skin (3%). Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with BAT. The fatal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningoencephalitis, and acute myocardial ischemia in <1% of patients each, respectively.

Permanent discontinuation due to an adverse reaction occurred in 15% of patients receiving VONJO 200 mg twice daily compared to 12% of patients treated with BAT. The most frequent reasons for permanent discontinuation in ≥2% of patients receiving VONJO 200 mg twice daily included anemia (3%) and thrombocytopenia (2%).

Drug interruptions due to an adverse reaction occurred in 27% of patients who received VONJO 200 mg twice daily compared to 10% of patients treated with BAT. The most frequent reasons for drug interruption in ≥2% of patients receiving VONJO 200 mg twice daily were anemia (5%), thrombocytopenia (4%), diarrhea (3%), nausea (3%), cardiac failure (3%), neutropenia (2%), and pneumonia (2%).

Dosage reductions due to an adverse reaction occurred in 12% of patients who received VONJO 200 mg twice daily compared to 7% of patients treated with BAT. Adverse reactions requiring dosage reduction in ≥2% of patients who received VONJO 200 mg twice daily included thrombocytopenia (2%), neutropenia (2%), conjunctival hemorrhage (2%), and epistaxis (2%).

The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

Table 5 summarizes the common adverse reactions in PERSIST-2 during randomized treatment.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VONJO (200 mg Twice Daily) (N=106)</th>
<th>Best Available Therapy (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades(^a)</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Anemia</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Urinating</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Dysnea</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\) Grade by CTCAE Version 4.03.
8 USE IN SPECIFIC POPULATIONS (cont.)

8.1 Pregnancy (cont.)
In a pre- and post-natal development study in mice, pregnant animals were dosed with pacritinib from implantation through lactation at 30, 100, or 250 mg/kg/day. Maternal toxicity was noted at 250 mg/kg and associated with increased gestation length and dystocia, lowered mean birth weights and neonatal survival, and transiently delayed startle response, learning, and memory development at weaning.

8.2 Lactation
Risk Summary
There are no data on the presence of pacritinib in either human or animal milk, the effects on the breastfed child, or the effects on milk production. It is not known whether VONJO is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with VONJO, and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential
Infertility
Males
Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib may impair male fertility in humans.

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

8.5 Geriatric Use
Clinical studies of VONJO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment
Administration of a single dose of VONJO 400 mg to subjects with hepatic impairment resulted in a decrease in the geometric mean AUC of pacritinib by 8.5%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C], respectively, compared to subjects with normal hepatic function. Avoid use of VONJO in patients with moderate [Child-Pugh B] or severe hepatic impairment [Child-Pugh C].

8.7 Renal Impairment
Administration of a single dose of VONJO 400 mg to subjects with renal impairment resulted in approximately 30% increase in C∞ and AUC of pacritinib in subjects with eGFR 15 to 29 mL/min and eGFR >15 mL/min on hemodialysis compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use of VONJO in patients with eGFR <30 mL/min.

17 PATIENT COUNSELING INFORMATION
See FDA approved patient labeling (Patient Information). Discuss the following with patient prior to and during treatment with VONJO:

Current therapy with another kinase inhibitor
Advise patients who are currently taking a kinase inhibitor that they must taper or discontinue their current kinase inhibitor therapy according to the package insert for that drug prior to starting VONJO.

Hemorrhage
Advise patients that VONJO can cause hemorrhage and instruct them to consult their healthcare provider right away if bleeding occurs. Advise patients about how to recognize bleeding and of the urgent need to report any unusual bleeding to their physician. Patients should urgently seek emergency medical attention for any bleeding that cannot be stopped.

Diarrhea
Advise patients that VONJO can cause diarrhea. Advise patients to stay hydrated while taking VONJO and to inform their physician if they experience diarrhea. Instruct patients to initiate antidiarrheal medications (eg, loperamide) if diarrhea occurs. Advise patients to urgently seek emergency medical attention if diarrhea becomes severe.

Thrombocytopenia
Advise patients that VONJO is associated with thrombocytopenia, and of the need to monitor complete blood counts before and during treatment.

Prolonged QT Interval
Advise patients to consult their healthcare provider immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of arrhythmia. Advise patients with a history of hypokalemia of the importance of monitoring their electrolytes.

Major Adverse Cardiac Events (MACE)
Advise patients that events of MACE including myocardial infarction, stroke, and cardiovascular death, have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not indicated. Advise patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis
Advise patients that events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not indicated. Advise patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Secondary Malignancies
Advise patients, especially current or past smokers and patients with a known secondary malignancy (other than a successfully treated NMSC), that lymphoma and other malignancies (excluding NMSC) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not indicated.

Infections
Advise patients that treatment with another JAK inhibitor has increased the risk of serious infections in patients with myeloproliferative neoplasms and that serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Inform patients of the signs and symptoms of infection and to report any such signs and symptoms promptly.

Nausea and Vomiting
Advise patients that nausea and vomiting may occur during treatment with VONJO. Instruct them on how to manage nausea and vomiting and to immediately inform their healthcare provider if nausea/vomiting become severe.

Drug-Drug Interactions
Advise patients to inform their healthcare providers of all medications they are taking, including prescription and over-the-counter medications, vitamins, herbal products, and dietary supplements.

Dosing
Advise patients to take VONJO twice a day, with or without food or drink, at similar times each day. Instruct patients to swallow the VONJO capsules whole and not to open, break, or chew the capsules. Instruct patients that if they miss a dose of VONJO, to skip the dose and take the next dose when it is due and return to the normal schedule. Warn patients not to take 2 doses to make up for the missed dose. Instruct patients to discontinue VONJO 7 days prior to any surgery or invasive procedures (such as cardiac catheterization, coronary stenting, or varicose vein ablation) due to the risk of bleeding and to only restart VONJO on the instruction of their healthcare provider. Patients should not change or stop taking VONJO without first consulting their physician.

Lactation
Advise patients to avoid breastfeeding while taking VONJO and for 2 weeks after the final dose.

Additional information can be found at VONJO.com.

Manufactured and marketed by:
CTI BioPharma Corp.
3101 Western Ave #800
Seattle, WA 98121
VONJO™ is a trademark of CTI BioPharma Corp. ©2022 CTI BioPharma Corp. All rights reserved.
US-PAC-2100050 02/2022
Kim and Schwartz Break Down the Role of Radiation Segmentectomy With Y-90 in Early-Stage HCC

by RYAN SCOTT

RETROSPECTIVE STUDIES HAVE POINTED to the benefits of radiation segmentectomy, a treatment that delivers yttrium-90 (Y-90) glass microspheres (TheraSphere) to a tumor in the liver, vs standard of care in patients with unresectable, very early-stage to early-stage hepatocellular carcinoma (HCC). Now prospective data have further clarified the benefit of this method, according to Edward Kim, MD, and Myron E. Schwartz, MD.

Data from the single-center, single-arm RASER trial (NCT03248375) showed that among 29 evaluable patients, radiation segmentectomy with Y-90 achieved an initial objective response in 100% of patients. Specifically, the complete response (CR) rate was 83%, and 17% of patients had a partial response. Notably, 90% of patients experienced a sustained CR.

“We developed [radiation segmentectomy] because there is a stage migration, and [clinicians] were using chemoembolization. But chemoembolization on explant tissue historically has had about 50% correlation with pathologic necrosis,” Kim said. “Radiation should be indiscriminate in terms of its destructive abilities. With chemoembolization, we don’t know if the drug matches a certain tumor type, but radiation and of itself should be indiscriminate. With a high enough dose, we should be able to get destructive radiation into target tissue. We devised this protocol to go head-to-head with the ablation data to see if we can rival that type of data.”

In an interview with OncologyLive®, both Kim and Schwartz discussed the background and findings of the RASER study, the role of radiation segmentectomy, and its potential to be combined with immunotherapy. Kim is the director of interventional oncology, and assistant professor of radiology and surgery in the Division of Vascular and Interventional Radiology at Mount Sinai Medical Center in New York, New York. Schwartz is the director of liver surgery and the Henry Kaufmann Professor of Surgery at the Recanati/Miller Transplantation Institute at Mount Sinai Medical Center.

What is the standard of care for patients with unresectable HCC? What unmet needs exist for these patients?

Schwartz: Unresectable can mean more than one thing. It can mean either that the tumor is advanced in a way that it can’t technically be removed, or it can mean that the tumor, while it’s early, can’t be resected because it’s not safe. For the patients [with] early-stage [disease] who are not [eligible for] resection because of liver function, then liver transplantation is the standard of care. There’s a process of getting a patient to transplant that involves a variety of different modalities, chemoembolization, and microwave or radiofrequency ablation. We feel that radiation segmentectomy has a key role in this indication as well.

When it comes to the tumors that are unresectable because they’re more advanced, then it depends on whether the tumor is confined to the liver, in which case local regional treatments, chemoembolization, or radioembolization [are used]. However, it is not radiation segmentectomy in the same way that’s presented in the RASER trial, but [rather,] radiation [that includes] internal, external, or systemic therapy.

Now immunotherapy with the combination of durvalumab [Imfinzi] and bevacizumab [Avastin] has become a standard based on the [phase 3 EMERALD-2 trial (NCT03847428)], with data showing the combination had the best survival of any of the systemic combinations reported thus far.

Kim: I would agree with that sentiment. Unresectable HCC has a wide range of populations and can include, according to the BCLC [Barcelona Clinic Liver Cancer] guidelines, early stage all the way through the advanced stage. It is a big, heterogeneous population, and locoregional therapies can come into play in a certain subset. Systemic therapies come into play in the advanced subset.

Please expand on radiation segmentectomy and the mechanism of action of Y-90.

Kim: Radiation segmentectomy is a subselective injection of yttrium-90, which is a radiation source and a β emitter. The radiation only goes a short distance in soft tissue—approximately 3 mm—and is localized to where we inject our spheres that are embedded with Y-90. All the credit to our surgical colleagues, including Dr Schwartz, because radiation segmentectomy is similar in concept to an anatomic resection where we take a small, perfused area of the liver with radiation therapy.

I tell my patients that it’s similar to an anatomic resection, except we’re not removing tissue but injecting a high dose of radiation spheres into the area and destroying it.

Schwartz: As far as the mechanism is concerned, it’s straightforward. It is similar in concept to resection. It has been an evolution in our practice in terms of where we use radiation segmentectomies, as it’s been proven to be effective, to the point where we are now starting to apply it in patients who might be resectable but are not the most ideal resection candidates [because of] an increase in confidence based on the results of the RASER trial.

Similar to surgery, for which we undergo a 5-year residency and a 2-year fellowship, this is a technique that took a period of years to be developed to the point where it is as good as...
it is now. This is credited to Dr. Kim, as it is a procedure that takes a high level of expertise on the part of the radiologist to do it reliably and consistently to the point where we can count on it as an alternative to something like resection.

**Q** What were the objectives of the RASER trial?

**KIM:** Dr. Schwartz and I, along with other investigators, developed this protocol together because there was an unmet need. At that time, any patient that could go to surgical resection would go to surgical resection. But not everyone is resectable, for one reason or another. The other gold standard is thermal ablation, but it’s limited in its efficacy based on location, adverse effects, or inefficiency of the ablation, as well as the size of the lesion.

**SCHWARTZ:** This technique, radioembolization, is not a new thing. It’s been around for 25 or 30 years, but it became popular over recent years, [now] using it the way that Dr. Kim has. It is a versatile technique. This application [in the RASER trial] may be the best. It’s very impressive, now that it’s been developed to this level, how consistent the results are. Our liver cancer program relies on it a lot.

**Q** How was radiation segmentectomy evaluated in the target patient population of the trial?

**KIM:** The target population is [patients with] solitary lesions up to about 3 cm without any extra hepatic spread or vascular invasion, very early to early HCC with a Child-Pugh A score and excellent performance status. In terms of evaluating its efficacy, we performed a pre- and post-MRI, as well as quantified how much dose was delivered to the patient with a PET [positron emission tomography] CT. This was the only prospective trial that evaluated post-Y-90 PET CT dosimetry. We had some very good metrics to quantify the amount of radiation and the targeting that was available for these patients. The goal was curative intent, though we rely on this heavily to bridge our patients to transplantation.

**SCHWARTZ:** The patients were, in some cases, candidates for transplantation who needed to be bridged to transplant and in other cases, [older] patients who were not ideal candidates for resection. They all had normal liver function. That was part of the trial because we were setting this trial up to be a comparison with the trials of ablation and even to compare with the data on ablation and even to compare with the data on transplantation. They all had normal liver function. That was important.

Eight patients then went on to transplantation with explant tissue, and all 8 patients who had CR on imaging also had complete pathologic necrosis. There was a concordance between the radiologic-pathologic findings, and it was shown to be safe, with mostly grade 1 toxicities, such as fatigue and nausea, which is what we’ve found over the past decade when we perform this therapy.

**Q** Was there anything else notable regarding safety and toxicity?

**KIM:** It is important to note what has been reported before with radioembolization in multiple studies, which has just been nausea, some vomiting, and fatigue, though [we observed] a very low incidence of any type of toxicity—usually grade 1 events. [Patients] don’t get the pain or postembolization syndrome that patients get with chemoembolization, as Y-90 is more reliant upon the radioembolization, or radiation, and not so much the blocking off of arteries.

**SCHWARTZ:** This is one of the advantages, that it’s an ambulatory procedure. Patients can come and go home, and they don’t remain in the hospital. It’s very appealing from the patient’s perspective.

**Q** How does the study support the inclusion of the approach for early-stage HCC in BCLC guidelines?

**KIM:** It was incorporated into the BCLC guidelines in 2022, based off a multicenter retrospective analysis from the [retrospective] LEGACY study, but there were no prospective data for this technique. The RASER study validates the findings of the LEGACY study and the inclusion into the BCLC guidelines with the prospective phase 2 data. We are quite proud of validating that data set prospectively.

**SCHWARTZ:** There still may be a bit of work to do. If you look in the BCLC where radioembolization is placed in the intermediate-stage patients, [radiation segmentectomy] is not yet in the BCLC guidelines up against resection or microwave radiofrequency ablation as a treatment for early-stage disease. The RASER trial, in our minds, puts it there based on not just the trial, but our experience overall with this technique.

In order to get into guidelines, you need a trial of more than 29 patients. We are familiar with the guidelines, since the person who creates the BCLC is our director of research at Mount Sinai, Josep Llovet, MD. [Radiation segmentectomy] is increasingly accepted around the country. The RASER study has had a big impact, but it’s not listed in the BCLC as an alternative to resection, which in our minds it is.

**KIM:** It is listed in the early stage after resection and ablation if those are not feasible, but we’re potentially moving into the space where we could use it as an alternative to resection or ablation.

**Q** How does this add to what was observed in the LEGACY study?

**KIM:** It validates it with a prospective analysis of this data set. Moreover, we also have a pathology correlation, showing that high doses that were delivered to the target area resulted in complete pathological necrosis.

**Q** Dr. Schwartz, what considerations do you have as a surgeon for the patient population, and how would this fit in with immunotherapy?

**SCHWARTZ:** That is a big and interesting question. Radiation segmentectomy is a treatment that’s applied to early-stage tumors, and we use it. We’ve already talked about it in patients who are awaiting transplantation, who need their tumor controlled until they can get there, and in patients who are early stage and maybe not transplant candidates based on their age or other considerations but who are not optimal resection candidates. In patients who are optimal resection candidates, I tell them that we can remove this—and that’s been the standard for years—but [that] we have a treatment that we’ve been developing that has been tested and doesn’t involve surgery. And we explain what the data are.

[For some of the patients who are candidates for resection, especially for tumors that are in locations that we can’t remove easily with a minimally invasive approach, we’ll choose the nonsurgical treatment, radiation segmentectomy, recognizing that [the] likelihood of complete destruction of the tumor [may be a few percentage points lower]. However, patients don’t have to have their [abdomen] cut open, and it’s often a reasonable trade-off.

When it comes to the role of systemic therapy, systemic therapy is a treatment for what’s traditionally been applied in advanced disease. As it’s been showing its benefit, we’re starting to apply it in earlier-stage disease. We have trials open using immunotherapy prior to resection in the neoadjuvant setting to try to lower the incidence of recurrence of cancer.

The same concept applies with radioembolization because there is a lot of interest in the idea that radiation has the ability to affect the tumor in a way that it releases antigens and proteins from the tumor that may help the immune
system recognize the tumor. It may have a role together with immunotherapy.

Dr Kim has been working to get a trial open combining radioembolization and immunotherapy. The concept of radiation segmentectomy plus immunotherapy is analogous to our resection trials, but the bigger role may be in the patients with more advanced disease who have tumors in the liver that are advanced, which are indicated for systemic therapy but may be very nicely augmented by radioembolization.

Dr Kim, what role do you see Y-90 playing in combination with immunotherapy for patients with unresectable HCC?

KIM: Not within the context of the RASER study, but I agree with Dr Schwartz that outside of that patient population, we envision radioembolization playing a role in the various stages of the BCLC [guidelines]. In the advanced stage, especially in individuals with vascular invasion or a hypervascular tumor, we should be able to target and deposit the Y-90 spheres into the tumor and the tumor thrombus and cause destruction, as well as prevent progression.

We like to combine the therapies for an immunomodulatory effect, as Dr Schwartz has described, in conjunction with checkpoint inhibitors. When you look at the phase 3 IMbrave150 trial [NCT03434379], approximately 33% to 35% of patients had an objective response to the systemic therapy. And with radioembolization, achieving higher objective response rates, particularly with hypervascular tumors with vascular invasion, can potentially improve median overall survival, as objective response has been used as a surrogate for survival benefit.

Overall, we’re hoping to get higher objective response rates and improve upon atezolizumab/Tecentriq/bevacizumab in the advanced population. We’re also interested in the potential downstaging population, especially individuals that have an aggressive tumor biology. Can we potentially downstage these patients with Y-90 to within UNOS [United Network for Organ Sharing] T2 criteria, and then add adjuvant checkpoint inhibitors to give those patients a chance at a true curative therapy, which would be transplantation? We’re also investigating that potential role.

What are the key takeaways regarding what was observed with Y-90 in this trial?

SCHWARTZ: The RASER trial advances what we’ve been seeing and doing at Mount Sinai. The idea is that radiation segmentectomy is truly an ablative technique that is analogous to thermal ablation and even resection and its ability to reliably destroy the tumor that’s being targeted. It needs to be considered among alternatives for patients. The choice of which one to use is based on technical issues, the location of a tumor, and the condition of the liver. However, it’s right there and should be advanced into the consideration for first-line treatment of early-stage tumors.

KIM: Ultimately, patients benefit from these data, which we’ve been using at Mount Sinai for almost a decade now. Patients have been benefiting because they have alternatives now, as not everyone’s a resection candidate. Ablation can be considered, but not everyone’s an ablation candidate. After that, oncologists didn’t have many options in terms of a curative intent treatment, but now they do. Ultimately, patients benefit with curative-intent treatments for this subset of the population.

What is significant about this data set vs other data sets that have previously read out in this space?

KIM: For this particular subset of patients with very early- to early-stage [disease] that were included in this study, none of the studies previously were prospective in their analysis of this data set. We had a 2-year follow-up, which presented strong data that validate what we’ve been practicing for many years.

There have been retrospective studies, but those are always open to criticism because of the retrospective nature. However, this is a prospective data set.

What are the next steps in the research for radiation segmentectomy and the use of Y-90?

SCHWARTZ: Radioembolization got started in an interesting way. The companies that provide it have always been reluctant to do large-scale, randomized trials putting it up against other treatments. It has gotten to where it is based on retrospective data and now prospective data. The obvious answer would be a large, randomized trial, but I don’t believe that’s going to happen.

I believe that the evidence has been building, notwithstanding the absence of randomized trials, that this is an effective treatment, and companies are now looking to do a large phase 3 trial, putting radiation segmentectomy up against embolization. The different treatments that we have each have their application. Like Dr Kim said, there are some patients where the tumor is in a place that we can’t get via radiation or ablation. They each have a role.

Combining radiation with other modalities to try to increase the cure rate [could be the next step]. The trouble with HCC is whatever is done to the index tumor, there’s a greater than 50% recurrence rate over the first 5 years because that’s the nature of the tumor. Patients also have a tendency to develop other tumors because they generally have underlying liver disease. The research has [shown] that the treatment of that tumor works, and we have to start looking at what we can do to maintain the response with immunotherapy and other modalities to try to cure not only the individual tumor that we were able to destroy, but to leave the patient free of cancer and able to live out their natural life span without HCC.

KIM: I agree with you. The easy answer that everyone gives is that we now need to expand to phase 3 studies, but that is not necessarily the realistic or correct answer. I don’t know if we need to go on to a phase 3 study, but I’d like to see the role of Y-90 expand and be validated in the roles of downstaging and in the intermediate stage, which is also a heterogeneous population similar to the advanced stage. The excitement is in combining [Y-90] with checkpoint inhibition, though not all patients respond to checkpoint inhibitors, and not everyone responds to radioembolization.

Radioembolization is a holdover for certain patients who may have good or aggressive tumor biology. We need to get to the core and try to help those individuals across all their tumor biology types. We can’t forget that there’s also a competing cause of mortality, which is cirrhosis, in this patient population.

Until we can reverse cirrhosis with medication, there will always be the role of transplantation because we can treat the HCC. We have seen patients where we have treated their HCC and they responded well to local regional or systemic therapy, but then the cirrhosis may progress, decreasing their life expectancy. I’d like to see combination trials examine the role of radioembolization in combination with an agent that can treat underlying cirrhosis.

REFERENCE

Epcoritamab Elicits Impressive Responses in Relapsed/Refractory LBCL

by KYLE DOHERTY

THE FIRST-IN-CLASS, SUBCUTANEOUSLY administered T-cell-engaging bispecific antibody epcoritamab demonstrated deep and durable responses in patients with relapsed/refractory large B-cell lymphoma (LBCL), according to pivotal dose-expansion results from the LBCL cohort of the phase 2 EPCORE NHL-1 trial (NCT03625037). These findings were presented during the European Hematology Association Congress 2022.1

At the January 31, 2022, data cutoff, patients with LBCL who were treated with epcoritamab (n = 157) achieved an overall response rate (ORR) of 63% (95% CI, 55%-71%), including a complete response (CR) rate of 39% (95% CI, 31%-47%). Three percent of patients had stable disease, and 24% experienced disease progression. Additionally, the median overall survival (OS) was not reached (NR), and the 6-month and 12-month OS rates were 70.6% (95% CI, 62.7%-77.2%) and 56.9% (95% CI, 47.3%-65.4%), respectively.

Notably, the median duration of response (DOR) for patients who experienced a CR was NR. The median time to CR was 2.7 months (range, 1.2-11.1). Overall, the median DOR was 12.0 months (range, 0+ to 15.5+) and the median time to response was 1.4 months (range, 1.0-8.4). The median follow-up time was 10.7 months (range, 0.3-17.9).

“Epcoritamab is a novel, subcutaneous bispecific antibody in development,” Catherine Thieblemont, MD, PhD, head of the hematopathology department at Hôpital Saint-Louis, in Paris, France, said in a presentation of the findings. “We know relapsed and refractory LBCL is a difficult disease with a poor prognosis. The EPCORE NHL-1 dose-escalation cohort has been reported and published, with notable activity with clinically meaningful overall and CR rates as a single agent.”

The EPCORE NHL-1 trial enrolled patients with relapsed/refractory, CD20-positive mature B-cell neoplasms. Eligible patients had an ECOG performance status of 0. The median age of patients in the LBCL cohort was 64 years (range, 20-83). Half of the cohort had an ECOG performance status of 2 or less and underwent at least 2 prior lines of therapy, including at least 1 anti-CD20 monoclonal antibody. Prior treatment with chimeric antigen receptor (CAR) T-cell therapy was permitted.

Patients received subcutaneous epcoritamab at the recommended phase 2 dose of 48 mg weekly during cycles 1 through 3, biweekly during cycles 4 through 9, and 4 times per week during cycle 10 and beyond. Treatment continued until disease progression or unacceptable toxicity. Inpatient monitoring was required at the first full dose for 24 hours.

The LBCL cohort included patients with diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), and follicular lymphoma (FL) grade 3B.

The primary end point was ORR by independent review committee. Key secondary end points included DOR, time to response, OS, CR rate, progression-free survival (PFS), and safety/tolerability.

The median age of patients in the LBCL cohort was 64 years (range, 20-83). Half of the cohort had an ECOG performance status of 1 and 47% had a performance status of 0.

Most patients in the cohort had DLBCL (89%), including 70% with de novo DLBCL. Nine patients had HGBCL, 4 had PMBCL, and 5 had FL grade 3B.

The median number of prior lines of therapy was 3 (range, 2-11), and 71% of patients had at least 3 prior lines of treatment. Most patients had primary refractory disease (61%) and most patients were refractory to their most recent systemic therapy (83%). Prior CAR T-cell therapy was reported in 39% of patients, and 75% progressed within 6 months of CAR T-cell therapy.

At the data cutoff date, 32% of patients were continuing with treatment and 68% had discontinued treatment. Reasons for treatment discontinuation included progressive disease (53%), adverse effects (AEs; 7%), allogenic stem cell transplant (4%), withdrawal by patient (3%), and other reasons (1%).

Further data from the trial showed that responses were consistent across key subgroups: patients experienced an ORR of at least 46% regardless of age, disease histology, CAR T-cell therapy exposure, or number of prior lines of treatment. Notably, patients who were CAR T-cell therapy naïve (n = 90) achieved an ORR of 69% with a CR rate of 27%. Patients who were at least 75 years old (n = 29) and those with transformed DLBCL (n = 40) also had particularly high response rates, with ORRs of 72% and 68%, respectively.

The median PFS for complete responders was NR, and 89% of complete responders remained in CR at 9 months. The overall median PFS was 4.4 months (95% CI, 3.0-7.9), and the overall PFS rate at 6 months was 43.9% (95% CI, 35.7%-51.7%).

Additionally, an exploratory circulating tumor DNA analysis showed that minimal residual disease (MRD)-negative responses were durable and correlated with PFS. Among 107 evaluable patients, the MRD-negative rate was 45.8% (95% CI, 36.1%-55.7%).

In terms of safety, most AEs were low grade and occurred during the first 3 treatment cycles. Common AEs of any grade included cytokine release syndrome (CRS; 49.6%), neutropenia (28%), pyrexia (23.5%), and fatigue (22.9%). Ten patients experienced immune effector cell-associated neurotoxicity syndrome (ICANS) of any grade; 9 of these were grade 1 or 2 and resolved, and 1 patient experienced grade 5 ICANS.

CRS events were primarily low grade and predictable; 31.8% of patients who experienced CRS had a grade 1 event, 15.3% had a grade 2 event, and 2.5% had a grade 3 event. The median time to onset of CRS from the first full dose was 20 hours, and 98.7% of patients had their CRS resolved. The median time to resolution from the first full dose was 48 hours, and CRS led to treatment discontinuation in only 1 patient.

“Epcoritamab is well tolerated and drives deep and durable responses in this cohort of patients with challenging-to-treat relapsed/refractory LBCL,” Thieblemont said.

REFERENCE
Obinutuzumab/Chemo Maintains Superior PFS in Untreated Follicular Lymphoma at 7 Years

by JASON HARRIS

THE COMBINATION OF OBINUTUZUMAB (Gazyva) plus chemotherapy delivered a superior long-term progression-free survival (PFS) benefit for patients with treatment-naive follicular lymphoma (FL), according to final analysis of the phase 3 GALLIUM trial (NCT01332968). These findings were presented at the European Hematology Association Congress 2022.¹

At a median follow-up of 7.9 years (range, 0.0-9.8), the 7-year PFS for patients who received obinutuzumab/chemotherapy was 63.4% (95% CI, 59.0%-67.4%) compared with 55.7% (95% CI, 51.3%-59.9%) for patients who received rituximab (Rituxan) plus chemotherapy (HR, 0.77; 95% CI, 0.64-0.93; P = .006; TABLE 1).

"Meaningful improvement in PFS has been maintained with obinutuzumab/chemotherapy, with a 23% reduction in the risk of PFS and hazard ratio of 0.77, translating into longer time to next treatment," William Townsend, MD, a consultant hematologist at University College London Hospitals, in England, said in a presentation of the data. "This confirms again that the GALLIUM trial represents another step forward in the treatment of previously untreated advanced stage [FL]. This is one of the largest trials assessing the value of end of induction PET, and these long-term data confirms the predictive value of that for both PFS and overall survival.²

In GALLIUM, investigators randomly assigned 1202 patients with previously untreated FL to induction therapy with obinutuzumab/chemotherapy (n = 601) or rituximab/chemotherapy (n = 601). Patients then received 2 years of maintenance therapy with the same induction agent.

The median age was 60 years (range, 26-88) in the obinutuzumab arm and 58 years (range, 23-85) in the rituximab arm. Most patients were women in both arms. In the experimental arm, 78.7% had intermediate- or high-risk disease by Follicular Lymphoma International Prognostic Index score, as did 79.2% of the patients in the control arm.

An interim analysis performed at a median follow-up of 34.5 months (range, 0-54.5), showed a 3-year PFS rate of 80.0% with obinutuzumab compared with 73.3% with rituximab (HR, 0.66; 95% CI, 0.51-0.85; P = .001). Response rates were also similar between the 2 groups, at 88.5% and 86.9%, respectively.³ At a median follow-up of 57.3 months, obinutuzumab-based therapy was associated with a 4-year PFS rate of 78.1% compared with 67.2% with rituximab-based therapy (HR, 0.73; 95% CI, 0.59-0.90; P = .0034). The 4-year overall survival (OS) rates were similar, at 92.6% and 90.3%, respectively.³

In this final analysis, Townsend said obinutuzumab improved 7-year PFS across most subgroups, although results in those with low-risk disease slightly favored rituximab (65.4%) vs obinutuzumab (70.9%; HR, 1.20; 95% CI, 0.75-1.90; P = .45). In patients with intermediate- or high-risk FL, the 7-year PFS rate was 62.9% vs 51.8% (HR, 0.70; 95% CI, 0.57-0.86; P < .001) favoring obinutuzumab.

Townsend noted that obinutuzumab improved time to next lymphoma treatment (NLT). There were 160 (26.6%) NLT events in the experimental arm compared with 209 (34.8%) in the control arm. Furthermore, patients assigned to obinutuzumab were more likely to be free from NLT at 7 years (74.1% vs 65.4%; HR, 0.71; 95% CI, 0.58-0.87; P = .001).

"One potential criticism of PFS as the primary end point in first-line [FL] studies is that these patients underwent numerous scans at various time points after completing therapy, and perhaps you pick up a number of progresses, radiologically, that are not clinically significant in [FL]," Townsend said. "It is reassuring to see that the perhaps more subjective but clinically meaningful end point of time to next treatment is similarly improved with obinutuzumab, with a similar order of magnitude as the PFS benefit.

The 7-year OS rates were similar with obinutuzumab and rituximab, at 88.5% (95% CI, 85.6%-90.9%) and 87.2% (95% CI, 84.1%-89.7%), respectively (HR, 0.86; 95% CI, 0.63-1.18; P = .36).

PET response status at end of induction (EOI) was associated with improved survival. Investigators performed a retrospective analysis of 519 patients who underwent PET at EOI. Patients who had complete metabolic response (CMR) had superior 7-year PFS (57.2% vs 26.5%; HR, 0.31; 95% CI, 0.22-0.46; P < .0001) compared with those who did not, and the result was similar for OS (90.2% vs 73.2%; HR, 0.30; 95% CI, 0.18-0.52; P < .0001).

Townsend noted that those who had CMR with obinutuzumab also had superior PFS results for those who did so with rituximab. The 7-year PFS rate for those who had CMR on obinutuzumab was 62.5% compared with 51.4% for rituximab (HR, 0.72; 95% CI, 0.52-0.99; P = .04). OS results following CMR were similar irrespective of treatment (90.6% vs 89.8%; HR, 1.09; 95% CI, 0.61-1.93; P = .77).

"[Patients] who did not achieve metabolic remission is a relatively small group and therefore confidence intervals are wide," Townsend said. "But again, it appears that those patients not achieving metabolic remission in [the] obinutuzumab arm may derive more benefit than the induction [with rituximab]."

The rates of grade 3 or higher adverse effects (AEs) and serious AEs were 79.2% and 48.7% in the obinutuzumab arm vs 71.2% and 42.2% with rituximab-based therapy at the 4-year follow-up. No new safety signals were reported.

In the observation/follow-up phase, 21.3% of patients in the experimental arm had experienced grade 3 or higher AEs and 17.2% have experienced serious AEs. Those results are 15.7% and 14.5%, respectively, in the rituximab arm.

No grade 3 or higher infusion-related reactions were reported in this phase. In the experimental arm, investigators observed grade 3 or higher neutropenia in 3.5% of patients and grade 3 or higher infections in 8.7%. In the control arm, these rates were 1.7% and 5.8%, respectively.

TABLE. Efficacy in the GALLIUM Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Obinutuzumab plus chemotherapy (n = 601)</th>
<th>Rituximab plus chemotherapy (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-year PFS (95% CI)</td>
<td>63.4% (59.0%-67.4%)</td>
<td>55.7% (51.3%-59.9%)</td>
</tr>
<tr>
<td>7-year OS (95% CI)</td>
<td>88.5% (85.6%-90.9%)</td>
<td>87.2% (84.1%-89.7%)</td>
</tr>
<tr>
<td>Patients free from NLT at 7 years (95% CI)</td>
<td>74.1% (70.3%-77.5%)</td>
<td>65.4% (61.4%-69.2%)</td>
</tr>
</tbody>
</table>

NLT, next lymphoma treatment; OS, overall survival; PFS, progression-free survival.
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 toxicity⁷

*Median DFS was not reached for TAGRISSO (95% CI: 58.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.¹

†Control arm=placebo.

²Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.22 (95% CI: 0.15, 0.30).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 (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
• Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases

• There are no contraindications for TAGRISSO

• TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer

INDICATION

OVERWHELMING EFFICACY
ADJUVANT TAGRISSO: DELIVERING FOR RESECTABLE EGFR m NSCLC

The first and only EGFR TKI to help prevent disease recurrence or death

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

• Patients in the

HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable;
CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive;
P

DFS Probability

or unacceptable toxicity1

ADAURA

0.0

0.4

1.0

0

PRIMARY ENDPOINT: DISEASE-FREE SURVIVAL IN PATIENTS WITH STAGE II/IIIA DISEASE (N=470)*

6 12 18 24 30 36 42 48 54

61%

28%

2-year DFS rate

3-year DFS rate

P<0.0001

(95% CI: 0.12, 0.23);

HR=0.17

REDUCTION IN RISK

83%

SELECT SAFETY INFORMATION

• Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-
treated patients in clinical trials, 0.8% were found to have a QTc >500 msec, and 3.1% of patients had an increase
from baseline QTc >600 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs
and electrolytes in patients with prolonged QTc interval, and discontinue TAGRISSO for those who develop signs/symptoms of QTc prolongation.

• Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A

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

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

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

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

• Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of
the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment.

• 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

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when after discontinuation of the strong CYP3A4 inducer

Interstitial Lung Disease/Pneumonitis

WARNINGS AND PRECAUTIONS

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

Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.

TAGRISSO is 80 mg tablet once a day. TAGRISSO can be taken with or without food. If the dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled. Treat patients in the adjuvant setting until disease recurrence, or unacceptable toxicity, or permanent discontinuation of TAGRISSO based on severity.

Cardiac[see Warnings and Precautions (5.2) in the full Prescribing Information] QTc interval prolongation

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to pregnant women. Use of TAGRISSO in pregnant women should only be considered if the potential benefit justifies the potential risk to the fetus. Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.

FDA-approved test[see Dosage and Administration (2.1) in the full Prescribing Information]

• Erythema multiforme and Stevens-Johnson syndrome

Postmarketing studies

Cytopenias[see Warnings and Precautions (5.5) in the full Prescribing Information]

Cytopenias[see Warnings and Precautions (5.5) in the full Prescribing Information]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of a different drug or to rates observed in clinical practice.

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

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematologic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>64/0.18 44/0.13</td>
<td>52/0.15 27/0.08</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>44/0.13 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26/0.08 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>25/0.08 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
<tr>
<td>Platelets</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Metabolic and Nutrient Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>35/0.13 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>22/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Cardiovascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>20/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Allergic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>22/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Eczema</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Infection and Infestation Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>20/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Metabolism and Nutrient Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>64/0.18 44/0.13</td>
<td>52/0.15 27/0.08</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>44/0.13 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26/0.08 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>25/0.08 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
<tr>
<td>Platelets</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Allergic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>22/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Eczema</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Allergic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>22/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Eczema</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Allergic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>22/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Eczema</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>TAGRISSO (N=337)</th>
<th>PLACER (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Allergic Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>22/0.06 10/0.03</td>
<td>14/0.04 10/0.03</td>
</tr>
<tr>
<td>Eczema</td>
<td>20/0.06 14/0.04</td>
<td>27/0.08 14/0.04</td>
</tr>
</tbody>
</table>
Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
<th>All Grades (3)</th>
<th>Grade 3 or higher (%)</th>
<th>All Grades (3)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>50</td>
<td>4.7</td>
<td>8</td>
<td>0.3</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24</td>
<td>2.2</td>
<td>4</td>
<td>0.7</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
<td>1.8</td>
<td>4</td>
<td>0.7</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>47</td>
<td>3.6</td>
<td>1</td>
<td>0.3</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyphocytes</td>
<td>49</td>
<td>3.6</td>
<td>9</td>
<td>1.5</td>
<td>9</td>
<td>1.8</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>50</td>
<td>4.7</td>
<td>6</td>
<td>0.7</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>17</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>0.7</td>
<td>9</td>
<td>1.8</td>
<td>9</td>
<td>1.4</td>
</tr>
</tbody>
</table>
EUROPEAN SOCIETY FOR MEDICAL
ONCOLOGY WORLD CONGRESS ON
GASTROINTESTINAL CANCER 2022
Barcelona, Spain
June 29-July 2, 2022

Tucatinib Plus Trastuzumab Induces Durable Tumor Response in HER2+ mCRC

by BRITTANY LOVELY

PATIENTS WITH PREVIOUSLY TREATED metastatic HER2-positive colorectal cancer (mCRC) experienced clinically meaningful and durable responses to treatment with tucatinib (Tukysa) plus trastuzumab (Herceptin) according to data from the phase 2 MOUNTAINEER trial (NCT03043313). These data were presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022.1,2

At a median follow-up of 20.7 months the confirmed objective response rate (ORR) among 84 patients who received the combination was 38.1% (95% CI, 27.7%-49.3%) as assessed by blinded independent central review (BICR) with a median duration of response (DOR) of 12.4 months (95% CI, 8.5-20.5). Further, the median progression-free survival (PFS) was 8.2 months (95% CI, 4.2-10.3) and the median overall survival (OS) of 24.1 months (95% CI, 20.3-36.7) (TABLE).1

“The patients with chemotherapy-refractory HER2-positive mCRC receive limited clinical benefit with currently available therapies,” John H. Strickler, MD, lead trial investigator and associate professor of medicine at Duke University School of Medicine, in Durham, North Carolina, said in a news release. “With sustained responses and favorable tolerability in heavily pretreated patients, tucatinib in combination with trastuzumab has the potential to be a new treatment option for previously treated HER2-positive mCRC.”

The pivotal MOUNTAINEER study was originally designed to include 1 cohort of patients to receive tucatinib at 300 mg twice daily and trastuzumab at 8 mg/kg intravenously on day 1 of cycle 1, followed by 6 mg/kg on day 1 of every 21-week cycle thereafter. Investigators adapted the protocol to enroll an additional 70 patients randomly assigned 4:3 to a new cohort of the experimental regimen or tucatinib monotherapy.3,4

The primary end point of the study was confirmed ORR in both experimental cohorts per BICR and RECIST 1.1. Secondary outcomes included ORR at 12 weeks, DOR, PFS, and OS in the experimental cohorts, safety, dose modifications, and laboratory results.1

The ORR at 12 weeks in a cohort of patients who were randomly assigned to tucatinib monotherapy (n = 30) was 3.3% (95% CI, 0.1-17.2), with a disease control rate of 80%. Of note, those who did not respond at 12 weeks or experienced disease progression were permitted to crossover to the experimental treatment.1,2

In terms of safety, commonly reported grade 1/2 treatment-emergent adverse effects (TEAEs) among patients who received tucatinib and trastuzumab (n = 86) were diarrhea (60.5%), fatigue (41.9%), nausea (34.9%) and infusion-related reaction (20.9%). Grade 3 or higher TEAEs included diarrhea (3.5%) and fatigue (2.3%). In terms of overall AEs observed on study, hypertension was the most common grade 3 or higher AE (7.0%).

No deaths were reported and 5.3% of patients discontinued treatment because of an AE. The most common grade 3 or higher 3 AE was hypertension (7.0%). AEs leading to discontinuation of any treatment occurred in 5.8% of patients. No deaths due to AEs were reported. Data from MOUNTAINEER will support a new drug application for patients with mCRC. In 2020, the FDA approved tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with advanced, unresectable, or metastatic HER2-positive breast cancer, including patients with brain metastases, who

TABLE. Primary Analysis of MOUNTAINEER

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tucatinib plus trastuzumab (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>38.1% (27.7%-49.3%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>12.4 (8.5-20.5)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.2 (4.2-10.3)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>24.1 (20.3-36.7)</td>
</tr>
</tbody>
</table>

DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
have received at least 1 prior anti–HER2-based regimens in the metastatic setting. 1

REFERENCES

Tislelizumab Plus Chemotherapy Elicits Strong Survival Benefit in Esophageal Cancer

by ASHLING WAHNER

THE COMBINATION OF TISLELIZUMAB (BGB-A317) and chemotherapy demonstrated a superior overall survival (OS) benefit compared with chemotherapy alone in patients with metastatic or unresectable esophageal squamous cell carcinoma (ESCC). In a presentation of data from the phase 3 RATIONALE 306 trial (NCT03783442) at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022, Harry H. Yoon, MD, said these data support the regimen as a new first-line option in this population.

The median OS was 17.2 months (95% CI, 15.8-20.1) with the addition of tislelizumab to chemotherapy vs 10.6 months (95% CI, 9.3-12.1) with chemotherapy alone representing a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.54-0.80; P < .0001).

An exploratory analysis showed that the combination elicited a significant improvement in OS regardless of PD-L1 expression. In patients with a combined positive score (CPS) of at least 10%, tislelizumab induced a median OS of 16.6 months (95% CI, 15.3-24.4) vs 10.0 months (95% CI, 8.6-13.0) in the control arm (HR, 0.62; 95% CI, 0.44-0.86, P = .0020). In those with CPS below 10%, the median OS was 16.7 months (95% CI, 13.0-20.1) vs 10.4 months (95% CI, 9.1-13.0) in favor of tislelizumab (HR, 0.72; 95% CI, 0.55-0.94).

The survival benefit associated with tislelizumab was consistent across all other subgroups including race, geographical region, and investigator choice of chemotherapy.

“These data [introduce tislelizumab as] a third anti–PD-1 antibody that’s been tested in the global population as a potential frontline option for patients with advanced ESCC,” Yoon said.

In an interview with OncologyLive®, Yoon, an associate professor of oncology and a consultant in the Division of Medical Oncology in the Department of Oncology at Mayo Clinic in Rochester, Minnesota, discussed the design of RATIONALE 306 and highlighted potential future directions for tislelizumab and other novel therapies in ESCC.

What was the impetus for combining tislelizumab with chemotherapy in RATIONALE 306?

One of the hypotheses was that when you add a PD-1 blockade to chemotherapy, the 2 cooperate with each other. There were a few novelties about this trial. It was the first global trial [in advanced ESCC] where there was a real choice in chemotherapy. Prior global trials have looked at cisplatin plus fluoropyrimidine, whereas this global study looked at platinum/fluoropyrimidine as one choice and platinum/paclitaxel as another choice. So far, this is the only global study in the frontline setting for ESCC that allowed a choice of chemotherapy backbone.

This is also the only frontline study of ESCC that tested oxaliplatin specifically as a chemotherapy backbone for PD-1 blockade. This trial found that there appeared to be a similar level of benefit when PD-1 blockade, specifically tislelizumab,
was added with oxaliplatin-based chemotherapy as compared with cisplatin-based chemotherapy.

What were some key takeaways from this trial? The biggest finding was that tislelizumab plus chemotherapy showed a significantly better OS compared with placebo and chemotherapy. Specifically, the OS in the tislelizumab arm was 17.2 months vs 10.6 months in the placebo arm. That survival benefit was evident across different PD-L1 scores, including a PD-L1 score of 10 or higher vs less than 10. This benefit was also seen between geographic regions of Asia vs non-Asia and across investigator choices of chemotherapy.

Other findings showed that the addition of tislelizumab to chemotherapy significantly improved progression-free survival and overall response rates, and [the combination] increased duration of response.

What safety data were seen for the combination vs chemotherapy and placebo? [The combination has] a reasonable safety profile with no new safety signals [reported] and appeared to be well tolerated. The [rate of] grade 3 or higher toxicities in the tislelizumab arm was 67% vs 65% in the chemotherapy-alone arm.

What could these data mean for patients with metastatic or unresectable ESCC? Before this study began, the design was discussed with health care authorities and regulatory groups, including some in the United States. There’s a plan to submit these data to regulatory authorities, and if they are approved by guidelines and committees, then we could potentially offer another PD-1 blockade option in the frontline setting for patients with previously untreated ESCC.

How else could tislelizumab be used in this patient population? Tislelizumab has already been studied in the second-line setting, and it showed a significant benefit in that situation. This agent is also being tested in [several] other situations, including in nonmetastatic disease and in combination with other promising immunotherapy targets.

RECENT DATA SHOWED THAT a priming dose of tremelimumab added to regular-interval durvalumab (Imfinzi), also known as the STRIDE regimen, significantly improved overall survival (OS) compared with sorafenib (Nexavar) in the frontline setting for patients with unresectable hepatocellular carcinoma (HCC). The clinical benefit was observed irrespective of baseline albumin-bilirubin (ALBI) grade, according to updated data from the phase 3 HIMALAYA trial (NCT03298451) presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022 (World GI).

In patients with ALBI grade 1, the STRIDE regimen elicited a median OS of 23.43 months (95% CI, 19.19-28.75) compared with 19.02 months (95% CI, 15.67-23.16) for sorafenib (HR, 0.91; 95% CI, 0.71-1.15). In patients with ALBI grade 2/3, the median OS for durvalumab was 12.29 months (95% CI, 9.30-16.03) vs 9.72 months (95% CI, 7.23-11.76) for sorafenib (HR, 0.87; 95% CI, 0.69-1.09).

“We need to acknowledge that this was a post-hoc analysis, and all analyses that we have performed so far have been in respect to liver function, and they have never been prospectively evaluated,” Arndt Vogel, MD, PhD, said in an interview with OncologyLive®. “We have a very clear picture that liver function has a strong prognostic impact, which is important when we talk to our patients.”

Vogel is a managing senior consultant and professor in the Department of Gastroenterology, Hepatology, and Endocrinology and the head of the Gastrointestinal Cancer Center at the Hannover Medical School in Germany.

Tremelimumum/Durvalumab Produces Favorable OS Benefit in Unresectable HCC Irrespective of ALBI Grade

by RYAN SCOTT

What ongoing research in the field of esophageal cancer would you like to highlight? There are many interesting things going on in this space, particularly with immunotherapy. Some areas I’ve been interested in are how immunotherapy can cooperate with other therapies, particularly with antiangiogenesis therapies, and how it modulates the tumor microenvironment.

What were the unmet needs that the trial aimed to address? [Most] of our patients [receive a diagnosis] in an advanced setting. In early HCC, we can perform resection or liver transplantation, but when the tumor gets bigger, a patient [can present] with vascular infiltration or extra hepatic metastases. We are in a palliative setting, and for many years, we had few options. The major breakthrough came with immunotherapy-based combinations.
and this combination of PD-1 and CTLA4 antibodies is an important step for the armamentarium for advanced HCC.

**Q** What were the primary objectives of the HIMALAYA trial?
The HIMALAYA study was a 3-arm study looking at the combination of durvalumab and a single [dose] of tremelimumab, referred to as the STRIDE regimen. This was compared with sorafenib, with a primary end point of showing superiority [in efficacy]. The third arm [evaluated] durvalumab monotherapy. A key secondary end point [was] to show noninferiority compared with sorafenib.

This was a global study for patients with unresectable HCC who were not suitable for local regional therapies.

**Q** What were the key takeaways from the updated data?
The HIMALAYA study has been published as a full paper, and it was a positive study. For the STRIDE regimen, there was superior activity shown in terms of OS compared with sorafenib. Additionally, [single-agent] durvalumab was noninferior to sorafenib.

In HCC, we usually have 2 diseases [which include] chronic liver disease in many cases, such as liver cirrhosis, and the tumor. Based on past post-hoc analyses from phase 3 studies, liver function is a very important prognostic marker. At [2022 World GI], we analyzed the effect of liver function on OS for the 2 immunotherapy-based regimens. We grouped patients according to their liver function scores, which was part of the inclusion criteria.

To distinguish 2 groups of patients with different preserved liver function, we utilized the ALBI score: half of the patients were ALBI grade 1, with a good liver function, and the other half were ALBI grade 2/3.

We were able to show in the HIMALAYA study that liver function has a very important prognostic effect. The median OS was almost twice as long in patients with a more well-preserved liver function compared with those with ALBI grade 2.

In terms of efficacy, it was very evident that the STRIDE regimen has clear activity in both groups of ALBI grade 1 and ALBI grade 2/3. There was almost no significant difference in terms of the hazard ratio. We can say the prognostic impact of liver function was confirmed. Importantly, the STRIDE regimen was effective independent from the underlying liver function.

**What should be known regarding the safety profile and toxicities associated with the STRIDE regimen?**
In the HIMALAYA study, we saw the expected adverse effect [AE] profile, though we have slightly more AEs with the STRIDE regimen compared with the durvalumab monotherapy. There were more immune-related AEs [which required] more steroid use, but overall, there was no negative effect on the quality of life. In our analysis here, there was no impact of liver function on the safety profile for the patients.

**Based on the findings from this trial, what may shift in the treatment paradigm for patients with unresectable HCC?**
We need to acknowledge that this was a post-hoc analysis, and all analyses that we have performed so far have been in respect to liver function. They have never been prospectively evaluated. We have a very clear picture that liver function has a strong prognostic [capabilities], which is important when we talk to our patients.

In terms of efficacy, the data are not crystal clear. But for HIMALAYA, we can clearly conclude that more impaired liver function of ALBI grade 2/3 has no negative impact on the efficacy of durvalumab and tremelimumab. These data need to be confirmed in a real-world setting. But it is reassuring that we do not need to select our patients based on liver function when we consider the use of durvalumab or durvalumab/tremelimumab.

For a full list of references, see the article at OncLive.com.
Durvalumab Plus Chemotherapy Maintains OS Benefit in Advanced Biliary Tract Cancer

by CAROLINE SEYMOUR

THE ADDITION OF DURVALUMAB (Imfinzi) to gemcitabine and cisplatin demonstrated an improvement in overall survival (OS) vs gemcitabine and cisplatin plus placebo as frontline therapy in patients with advanced biliary tract cancer. Data from a subgroup analysis of the phase 3 TOPAZ-1 trial (NCT03875235) presented by Ao Wu Ruth He, MD, PhD, during the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022, confirmed this benefit regardless of tumor location.

Findings previously presented from the primary analysis demonstrated a 20% reduction in the risk of death with durvalumab plus chemotherapy vs placebo plus chemotherapy in this patient population (HR, 0.80; 95% CI, 0.66-0.97; P = .021).1

At a median follow-up of 13.7 months in the durvalumab/chemotherapy arm and 12.6 months in the placebo/chemotherapy arm, the median OS was 12.8 months (95% CI, 11.1-14.0) vs 11.5 months (95% CI, 10.1-12.5), respectively. The 18-month OS rates were 35.1% (95% CI, 29.1%-41.2%) and 25.6% (95% CI, 19.9%-31.7%), respectively. The 24-month OS rates were 24.9% (95% CI, 17.9%-32.5%) and 10.4% (95% CI, 4.7%-18.8%), respectively.

On May 4, 2022, the FDA accepted a supplemental biologics license application and granted priority review to the combination of durvalumab plus chemotherapy vs placebo plus chemotherapy in patients treated with the combination of durvalumab plus gemcitabine and cisplatin vs gemcitabine and cisplatin plus placebo.

I presented a subgroup analysis of the efficacy and safety data from the trial based on primary tumor location. Biliary cancer is a very heterogeneous disease that includes intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer. Each anatomic location can have different risk factors, etiology, and presentation or prognosis.

In this subgroup analysis of TOPAZ-1, the addition of durvalumab to gemcitabine and cisplatin was associated with improved OS in patients with advanced biliary tract cancer, irrespective of primary tumor location.

What are the next steps for research with this regimen?
I am very excited about additional biomarker analysis. Blood samples have been collected from patients enrolled in this study. In this cancer, there are a lot of potentially targetable mutations [because it’s] genetically very heterogeneous. There will be a lot of information we can learn [from these analyses]. Can we find patients with a certain genetic background or molecular profile that would benefit most from the combination therapy? That information also may teach us how to overcome resistance.

Within the scope of biliary tract cancer, what research are you excited to see develop?
I always talk about targeted therapy, because 40% to 50% of patients with biliary tract cancer may have targetable mutations. We keep identifying targetable mutations and [ways] to use targeted therapy to treat those patients with certain genetic alterations. We have FDA-approved agents for FGF2 fusions and IDH1/2 mutations. Now there are data coming out in BRAF-mutated cholangiocarcinoma [and] HER2-amplified biliary cancer. Those are always very exciting areas for [those] who treat patients with cholangiocarcinoma. We expect better targeted therapies to come out, and better selective biomarkers will define the patient population that responds to this therapy.

Second, durvalumab has shown—for the first time in the phase 3 TOPAZ-1 study—improved outcomes in combination with chemotherapy. I expect more work will be done with immune checkpoint inhibitors in cholangiocarcinoma evaluating dual immunotherapy and immunotherapy plus another targeted therapy in combination with chemotherapy. Also, the combination of durvalumab plus gemcitabine and cisplatin was quite well tolerated. Durvalumab did not increase toxicity much [in the trial]. This could be a good regimen to build on with additional immunotherapy in combination with the goal of improving patient outcomes.

The other thing that’s always exciting is circulating [tumor DNA (ctDNA)] biomarkers, because in cholangiocarcinoma it’s very difficult to get a lot of tissue to do profiling. Circulating biomarkers will help us identify mutations and track patients’ response to therapy and development of early resistance. There’s a lot of ongoing research [aiming] to make ctDNA markers work better for cholangiocarcinoma. Those are the 3 areas we’ll have a lot more information on in the next couple years.

What was the significance of the results interim analysis of TOPAZ-1?
The combination of cisplatin and gemcitabine had been the standard first-line therapy based on the phase 3 ABC-02 study [NCT00262769] for over a decade. TOPAZ-1 is the first positive, randomized, phase 3 study that has shown benefit of adding another drug to this standard chemotherapy combination.

The preplanned interim analysis of TOPAZ-1 showed the study met the primary end point. There was a statistically significant improvement in OS in patients treated with the combination of durvalumab plus gemcitabine and cisplatin vs gemcitabine and cisplatin plus placebo.

“Based on the subgroup analysis and the primary report, I feel comfortable recommending durvalumab plus gemcitabine and cisplatin as frontline systemic therapy.”
—AO WU RUTH HE, MD, PhD

For a full list of references, see the article at OncLive.com.
Botensilimab/Balstilimab Combo Produces Deep Responses in Microsatellite Stable CRC

by KRISTI ROSA

THE COMBINATION OF BOTENSILIMAB (AGEN1181) and balstilimab (AGEN2034) elicited deep objective responses with evidence of durability and encouraging tolerability in heavily pretreated patients with microsatellite stable (MSS), metastatic colorectal cancer (mCRC), according to expanded data from the phase 1b trial. C-800 study (NCT03860272).

Findings were presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022. At a median follow-up of 5.8 months (range, 1.6-24.4), the doublet elicited an objective response rate (ORR) of 24% (95% CI, 14%-39%) among 42 evaluable patients; this included a 24% partial response rate. Forty-nine percent of patients achieved stable disease with the regimen and 27% experienced disease progression.

Moreover, the median duration of response (DOR) was not reached with the combination. The disease control rate (DCR) reported with the doublet was 73% (95% CI, 58%-84%).

“CRC is the second leading cause of cancer-related death worldwide, with roughly 95% of cases classified as MSS and historically unresponsive to immunotherapy. Treatment-resistant MSS CRC patients lack effective options, with standard care offering only a 1% to 2% response rate and a median expected survival ranging from 6 to 7 months,” Anthony El-Khoueiry, MD, phase I program director at the University of Southern California Norris Comprehensive Cancer Center in Los Angeles, stated in a news release. “The robust response rate, durability, and tolerability demonstrated by botensilimab and balstilimab support further development of the combination in MSS CRC, as well as, more broadly, in other cold and treatment-resistant tumors.”

Enrollment criteria for the first-in-human trial required patients to have advanced solid tumors that were refractory to standard treatment. Individuals were permitted to have previously received immunotherapy. To be included in the CRC cohort, patients needed to have metastatic disease and MSS status per local assessment.

The efficacy end points of the trial include ORR, DCR, progression-free survival, DOR, and overall survival (OS). Key safety end points include adverse effects (AEs), treatment-related AEs, and immune-related AEs.

Among the 41 patients included in the MSS CRC cohort, the median age was 57 years (range, 36-82), 59% were female, 59% had an ECOG performance status of 1, and 34% received prior immunotherapy. The median number of prior lines of therapy received was 4 (range, 2-10); 12% of patients received 2 prior lines, 32% received 3 prior lines, 22% received 4 prior lines, and 34% received 5 or more prior lines. Fifty-one percent of patients had tumors that harbored a RAS mutation, and 5% harbored BRAF mutations (FIGURE).

Those in this cohort (n = 41) received the Fc-enhanced CTLA-4 inhibitor botensilimab at 1 mg/kg (17% of patients) or 2 mg/kg (83% of patients) every 2 weeks in combination with the PD-1 inhibitor balstilimab at 3 mg/kg every 2 weeks.

Additional data showed that 80% of objective responses were ongoing at the time of data cutoff, and 30% of objective responses exceeded 1 year.

Data from an exploratory analysis showed that those without active liver metastases (n = 24) experienced enriched responses with the combination. The ORR achieved with the combination was 42% (95% CI, 25%-61%) and the DCR was 96% (95% CI, 80%-99%) among these patients.

Any-grade treatment-related adverse effects (TRAEs) were experienced by 76% of patients; these effects were grade 1 or 2 in 51% of patients and grade 3 in 24% of patients.

The most common gastrointestinal toxicities reported with the doublet included diarrhea or colitis (grade 1/2, 29%; grade 3, 10%), nausea (grade 1/2, 17%), and vomiting (grade 1/2, 10%). Constitutional toxicities included fatigue (grade 1/2, 20%; grade 3, 2%), decreased appetite (grade 1/2, 22%), chills (grade 1/2, 17%), and pyrexia (grade 1/2, 12%; grade 3, 2%).

Hepatic toxicities included increased alanine aminotransferase (grade 1/2, 12%) and increased aspartate aminotransferase (grade 1/2, 7%; grade 3, 2%). Musculoskeletal effects include arthralgia (grade 1/2, 10%; grade 3, 2%) and myalgia (grade 1/2, 12%). Skin toxicities include pruritus (grade 1/2, 10%) and rash (grade 1/2, 10%).

No hypophysitis has been reported with the combination, and pneumonitis with the combination was noted to be rare. Notably, grade 4 or 5 TRAEs were reported with the regimen.

Investigator-assessed immune-related adverse effects (irAEs) of any grade occurred in 46% of patients, and 17% experienced grade 3 irAEs. Ten percent of patients discontinued botensilimab only due to a TRAE, and 10% discontinued both agents.

A global, dose-randomized, phase 2 trial examining the combination is anticipated to launch later in 2022.

REFERENCES


Do you have a patient with relapsed/refractory adult B-cell acute lymphoblastic leukemia?

We are conducting the single arm, open-label, multi-center phase 2 FELIX study (NCT04404660) to evaluate the investigational CD19 CAR T-cell product called AUTO1 (obecabtagene autoleucel or obe-cel) in patients with relapsed/refractory adult B-cell acute lymphoblastic leukemia. The primary objective of the study is to evaluate the safety and efficacy of AUTO1 given as a split dose on day 1 and on day 10. Following the initial dose of AUTO1, patients will be observed closely for at least 10 days in hospital. Patients will then be in follow-up until the end of the study. We are seeking assistance from referral centers and those physicians who treat adult B-ALL patients in regional community hematology/oncology clinics to help us identify qualified study participants.

clinicaltrials@autolus.com

www.autolus.com