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Toni Choueiri, MD, on GU MALIGNANCIES
Stephen Liu, MD, on LUNG CANCER
Michael Thompson, MD, PhD, on HEMATOLOGIC CANCERS
Tanios S. Bekaii-Saab, MD, on GI MALIGNANCIES

CLINICAL PERSPECTIVES
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By Renier J. Brentjens, MD, PhD; and Manjusha Namuduri, MD

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**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 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

**Hematologic adverse reactions** (thrombocytopenia, anemia, and neutropenia) 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

Please see additional Important Safety Information on the next page.
Important Safety Information (continued)

Hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary. **Embryo-Fetal Toxicity and Lactation:** Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose. **The most common adverse reactions** (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA included: thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

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

Please see Brief Summary on the following pages.


1L, first-line; PARP, poly (ADP-ribose) polymerase.

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**Table 1:** Recommended Dose Adjustments for Adverse Reactions

<table>
<thead>
<tr>
<th>Starting dose level</th>
<th>200 mg</th>
<th>300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>100 mg/day (one 100 mg capsule)</td>
<td>200 mg/day (two 100 mg capsules)</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>100 mg/day (one 100 mg capsule)</td>
<td>200 mg/day (one 100 mg capsule)</td>
</tr>
</tbody>
</table>

**Table 2:** Dosage Modifications for Non-Hematologic Adverse Reactions

- **CTCAE Grade 3: CTCAE Grade 3 adverse reactions that are non-hematologic are considered dose-limiting and may require dose modification.**
- **CTCAE Grade 4: CTCAE Grade 4 adverse reactions that are non-hematologic are considered life-threatening and may require discontinuation of treatment.**

<table>
<thead>
<tr>
<th>Dosage Adjustment</th>
<th>Description of Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First dose reduction</strong></td>
<td>ZEJULA decreased to a reduced dose per Table 1.</td>
</tr>
<tr>
<td><strong>Second dose reduction</strong></td>
<td>ZEJULA decreased to a reduced dose per Table 1.</td>
</tr>
</tbody>
</table>

**Table 3:** Common Terminology Criteria for Adverse Events

Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically thereafter. Also monitor platelet count and other hematologic parameters at least every 2 months. If a patient experiences a CTCAE Grade 3 or 4 adverse event, ZEJULA should be discontinued until the adverse event resolves. If the adverse event continues after ZEJULA has been discontinued, the dose should not be reduced further. If a patient experiences a CTCAE Grade 3 or 4 adverse event that improves or resolves, ZEJULA should be restarted at a reduced dose per Table 1. If the adverse event persists or worsens, ZEJULA should be discontinued. If the adverse event improves or resolves, ZEJULA may be restarted at a reduced dose per Table 1. If the adverse event persists or worsens, ZEJULA should be discontinued.

**Table 4:** Adverse Drug Reactions Reported in ≥15% of All Patients Receiving ZEJULA in Phase 2 Study

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZEJULA</strong></td>
<td><strong>Placbebo</strong></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>64</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>62</td>
</tr>
<tr>
<td>Enteric Fever</td>
<td>57</td>
</tr>
<tr>
<td>Constipation</td>
<td>52</td>
</tr>
</tbody>
</table>

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Zejula safely and effectively. See full prescribing information for Zejula available at www.Zejula.com.

**ZELIGA (niraparib) capsules, for oral use**

**INDICATIONS AND USAGE**

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

**Maintenance Treatment of Recurrent Ovarian Cancer**

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

**Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies**

ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more platin-based chemotherapies and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by one or more of the following:

- A deleterious or suspected deleterious BRCA mutation, or
- Germline instability and who have progressed more than six months after last systemic chemotherapy and platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

**DOSAGE AND ADMINISTRATION**

**Patient Selection for Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies**

Select patients for treatment of advanced ovarian cancer after three or more chemotherapies regimens associated with HRD positive status based on either deleterious or suspected deleterious BRCA mutation and/or germline instability status (GSI).

**Recommended Dosing**

Continue ZEJULA treatment until disease progression or unacceptable toxicities occur.

Instruct patients to take their dose of ZEJULA at approximately the same time each day. Advise patients to swallow each capsule whole and not to chew, crush, or split. ZEJULA is貂 not effective if the capsule is swallowed intact. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

For patients with body weight less than 77.5 kg (170 lb) and a platelet count of less than 150,000/µL, the recommended dose is 300 mg (two 150-mg capsules) taken orally once daily.

For patients weighing greater than or equal to 77.5 kg (170 lb) and with a platelet count of greater than or equal to 150,000/µL, the recommended dose is 600 mg (three 200-mg capsules) taken orally once daily.

**Maintenance Treatment of Recurrent Ovarian Cancer**

The recommended dose of ZEJULA is 300 mg (three 100-mg capsules) taken orally once daily.

**Dose Adjustments for Adverse Reactions**

- To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Tables 1 and 2.
- Do not reschedule within 28 days following intervention, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration).

**Cardiovascular Effects**

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

In PRIMA, Grade 3-4 hypertension occurred in 6% of ZEJULA-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range 1 to 54 days) and with a median duration of 12 days (range 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range 4 to 540 days) and with a median duration of 13 days (range 1 to 61 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRA, Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients with a median time from first dose to first onset of 13 days (range 1 to 116 days) and with a median duration of 7 days (range 1 to 138 days). Discontinuation due to hypertension occurred in <0.5% of patients.

ZEBULON, Grade 3-4 hypertension occurred in 15% of ZEJULA-treated patients with a median time from first dose to first onset of 13 days (range 1 to 116 days) and with a median duration of 7 days (range 1 to 138 days).

**Intermediacy of mechanism**

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman. ZEJULA has the potential to cause teratogenicity under embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals (e.g., mouse) (see Warnings and Precautions). Due to this risk, ZEJULA is a teratogenic to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Approse pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA (see Use in Specific Populations).

**ADVERSE REACTIONS**

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

- **Myelodysplastic Syndrome/Acute Myeloid Leukemia** (see Warnings and Precautions)
- **Bone Marrow Suppression** (see Warnings and Precautions)
- **Cardiovascular Effects** (see Warnings and Precautions)
- **Clinical Trials Experience**

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

**The most common adverse reactions at all grades in ≥10% of 12,134 patients who received ZEJULA in the pivotal PRIMA, NOVA and QUADRA trials were nausea (65%), vomiting (54%), fatigue (55%), constipation (39%), muscle spasms (38%), abdominal pain (38%), vomiting (38%), nausea (38%), fatigue (38%), nausea (38%), constipation (38%), diarrhea (21%), dehydration (18%), anemia (15%), fever (15%), diarrhea (15%), fever (15%), constipation (15%), and urinary tract infection (15%)

**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 phase III double-blind study in which 2,282 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range 0.9 to 39 months).

**All Patients Receiving ZEJULA in PRIMA**

Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in patients receiving ZEJULA included thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2%). Fatal adverse reactions occurred in 0.6% of patients, including intestinal perforation and bowel obstruction (one patient each). Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in ≥2% of patients who received ZEJULA included thrombocytopenia (2%), anemia (1%), nausea and neutropenia (1.3%), and pancreatitis (1.3%). Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (74%), anemia (93%), and neutropenia (20%).

Table 1 and Table 2 summarize the common adverse reactions and grade ≥3 laboratory abnormalities, respectively, observed in all patients treated with ZEJULA in the PRIMA study.
### Table 4: Adverse Drug Reactions Reported in ≥10% of All Patients Receiving ZELEUTA in PRIMA (continued)

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZELEUTA N=644</strong></td>
<td><strong>Placebo N=244</strong></td>
</tr>
<tr>
<td><strong>General Disorders and Adverse Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
</tr>
<tr>
<td>Investigations</td>
<td>14</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>35</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>25</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury*</td>
<td>12</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
</tr>
</tbody>
</table>

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

### Table 5: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELEUTA in PRIMA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZELEUTA N=644</strong></td>
<td><strong>Placebo N=244</strong></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>27</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 6: Adverse Drug Reactions Reported in ≥10% of Patients Receiving ZELEUTA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZELEUTA N=169</strong></td>
<td><strong>Placebo N=86</strong></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>46</td>
</tr>
<tr>
<td>Leukopenia*</td>
<td>28</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>39</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
</tr>
<tr>
<td><strong>General Disorders and Adverse Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
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<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury*</td>
<td>12</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
</tr>
</tbody>
</table>

*All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

### Table 7: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELEUTA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZELEUTA N=644</strong></td>
<td><strong>Placebo N=244</strong></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>70</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>63</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>60</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>43</td>
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<tr>
<td>Decreased magnesium</td>
<td>64</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
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</table>

### Table 7: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELEUTA Based on Baseline Weight or Platelet Count in PRIMA (continued)

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZELEUTA N=169</strong></td>
<td><strong>Placebo N=86</strong></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>28</td>
</tr>
</tbody>
</table>

### Table 8: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELEUTA in NOVA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZELEUTA N=97</strong></td>
<td><strong>Placebo N=39</strong></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>30</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17</td>
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<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>10</td>
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<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>74</td>
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<tr>
<td>Constipation</td>
<td>40</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34</td>
</tr>
<tr>
<td>Mucositis/montitis</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
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<tr>
<td>Mouth ulcers</td>
<td>10</td>
</tr>
<tr>
<td><strong>General Disorders and Adverse Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Anorexia</td>
<td>57</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25</td>
</tr>
<tr>
<td>Infections and infestations</td>
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</tr>
<tr>
<td>Urinary tract infection</td>
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<td><strong>Investigations</strong></td>
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<td>AST/A/L elevation</td>
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<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>18</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>10</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
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</tr>
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<td>Insomnia</td>
<td>27</td>
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<tr>
<td>Anxiety</td>
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</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
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<tr>
<td>Dysesthesia</td>
<td>20</td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>21</td>
</tr>
</tbody>
</table>
Table 4: Adverse Reactions Reported in ≥10% of Patients Receiving ZEFLURA in ZEPHYR (continued)

<table>
<thead>
<tr>
<th>Vascular Disorders</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

CTCAE = Common Terminology Criteria for Adverse Events version 4.02

Includes preferred terms of neutropenia, infection, neutropenic, and febrile neutropenia.

Table 5: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEFLURA in ZEPHYR

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in hemoglobin</td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72</td>
<td>21</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 6: Adverse Reactions Reported in >10% of Patients Receiving ZEFLURA in ZEPHYR (continued)

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemiaa</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Thrombocytopeniaa</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Neutropiaa</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

Gastrointestinal Disorders

| Nausea | 67         |
| Vomiting | 44         |
| Constipation | 36         |
| Abdominal pain | 34         |
| Diarrhea | 17         |

General Disorders and Administration Site Conditions

| Fatigue | 56         |
| Infections and Infestations | 15         | 2         |

Table 10: Adverse Reactions Reported in >10% of Patients Receiving ZEFLURA in ZEPHYR (continued)

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83</td>
<td>26</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 11: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEFLURA in ZEPHYR

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in hemoglobin</td>
<td>83</td>
<td>26</td>
</tr>
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<tr>
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<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
</tbody>
</table>

Postmarketing Experience

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

Zealand System Disorders: hypersensitivity (including anaphylaxis)

Neurologic System Disorders: posterior reversible encephalopathy syndrome (PRES)

Psychiatric Disorders: confusional state/delirium, hallucination, cognitive impairment

Respiratory, Thoracic, and Mediastinal Disorders: non-infectious pneumonitis Skin and Subcutaneous Tissue Disorders: pruritus/sensitivity

USE IN SPECIFIC PATIENTS

Pregnancy

Risk Summary

Based on its mechanism of action, ZEFLURA may cause fetal harm when administered to pregnant women. There are no data regarding the use of ZEFLURA in pregnant women to inform the drug-associated risk of birth defects or injury to the developing fetus. In rats, ZEFLURA increases fetal weight and decreases postnatal growth of pups. The background risk of major birth defects and miscarriage for the indicated population is unknown. In a small, uncontrolled study, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies was 2% to 4% and 15% to 20%, respectively.

Lactation

Risk Summary

No data are available regarding the risk of nevirapine or its metabolites in human milk on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZEFLURA, a lactating woman not to breastfeed during treatment with ZEFLURA and for at least 6 months following the last dose.

Females and Males of Reproductive Potential

Pregnancy Risk

ZEFLURA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). A pregnancy test is recommended for females of reproductive potential prior to initiating ZEFLURA treatment.

Contraception

Females

ZEFLURA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations).

Advisories for use in reproductive potential to use effective contraception during treatment with ZEFLURA and for at least 6 months following the last dose.

Infertility

Males

Based on animal studies, ZEFLURA may impair fertility in males of reproductive potential.

Pediatric Use

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

Geriatric Use

In PRIMA, 15% of patients were aged ≥66 years and 10% were aged ≥75 years. In ZEPHYR, 35% of patients were aged ≥65 years and 5% were aged ≥75 years. No overall differences in safety and effectiveness of ZEFLURA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dose adjustment is necessary for patients with mild (Clcr 60 to 85 mL/min) to moderate (Clcr 30 to 59 mL/min) renal impairment. The dose of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEFLURA was not altered in patients with moderate to severe renal impairment.

Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute–Drug Interactions Working Group criteria. The dose of hepatic impairment was determined by the drug-specific hepatic function as estimated by the United States Adopted Medical Terminology (USAMT) classification.

In patients with moderate to severe hepatic impairment, no dose adjustment is required.

There is no specific treatment in the event of ZEFLURA overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION

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

Advises

Advises patients to contact their healthcare provider if they experience weakness, feeling tired, frequent weight loss, frequent infections, bruising, bleeding easily, (particularly in veins and life-threatening laboratory findings of low blood cell counts), or a need for transfusions. This may be a sign of hematological toxicity or myelosuppressive toxicity (OM3) or acute myeloid leukemia (AML) which has been reported in patients treated with ZEFLURA (see Warnings and Precautions).

Bone Marrow Suppression

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

Cardiovascular Effects

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

Using Instructions

Informs patients on how to take ZEFLURA (see Dosage and Administration).

ZEFLURA should be taken once daily in front of a monitor and if they miss a dose of ZEFLURA, not to take an extra dose to make up for the one they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEFLURA may be taken with or without food. Bedtime administration may be a potential option for managing nausea.

Embryo-Fetal Toxicity

Advises females to inform their healthcare provider if they are pregnant or may become pregnant. In females patients of the risk to a fetus and potential loss of the pregnancy (see Warnings and Precautions).

Contraception

Advises females of reproductive potential to use effective contraception during treatment with ZEFLURA and for at least 6 months after the last dose (see Use in Specific Populations).

Lactation

Advises patients not to breastfeed while taking ZEFLURA and for 1 month after the last dose (see Use in Specific Populations).

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PP-ZEFL-JUS-0996
NPBBF/S200003 May 2020
Produced in USA.

Manufactured by: GlaxoSmithKline
Research Triangle Park, NC 27709
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Findings from 3 studies with the potential to shake up the treatment landscape in several malignancies were among the highlights of the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. Experts discuss the impact of results from the ADAURA trial in non–small cell lung cancer, KEYNOTE-177 in colorectal cancer, and SOLO2 in ovarian cancer.
Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 72.
Innovation Thrives During the Pandemic

There’s nothing like the excitement of a major medical conference in the oncology arena, particularly the annual meetings of the American Society of Clinical Oncology (ASCO). More than 50,000 oncology and hematology specialists, investigators, and industry experts make the pilgrimage to Chicago, Illinois, each year to hear the latest research findings and network with their peers. The energy is always palpable; the discussions are always stimulating.

This year, of course, has been far different. The in-person meeting structure that supports so many of the continuing medical education opportunities in the oncology field started closing in mid-March because of the coronavirus disease 2019 (COVID-19) pandemic.

Like most other facets of the educational establishment, ASCO’s meetings had to pivot to an all-digital format. Nevertheless, the organization was able to offer a full menu of emerging research, as evidenced by the coverage in this issue of OncologyLive®. Our editorial team reports on practice-changing clinical study findings in our cover story, “3 Key ASCO Studies Showcase Targeted Advances,” and on expert insights across a range of malignancies in our Conference Highlights section.

Notably, however, the large medical associations weren’t the only groups that had to adapt rapidly to the COVID-19 world. In our Medical World News section, we describe the quick pivot from in-person to live, virtual events that Physicians’ Education Resource® (PER®), LLC, implemented. PER®, a member of MJH Life Sciences®, immediately launched a new, virtual, interactive series on the impact of COVID-19 on the treatment paradigm for specific cancer types. At the same time, the group transitioned its lineup of in-person meetings to live, interactive virtual formats.

Our content team has also stepped up its efforts to bring you the most up-to-date and important news. OncLive.com has provided full coverage of every major medical meeting and PER® conference since the pandemic began. We’ve also carved out a special section devoted to news, videos, webcasts, and expert insights into COVID-19. And we’ve launched a first-of-its-kind 24-hour Medical World News online program, available on OncLive.com, for health care professionals.

These projects aren’t just part of our business model at MJH Life Sciences®. They flow from our companywide commitment to provide the very best information possible to health care providers and patients alike.

We hope you find this information useful. We are always interested in hearing from you. Please email our editorial director, Gina Columbus, about the content you would like to see on OncLive.com and in our publications at gcolumbus@OncLive.com.

As always, thank you for reading—and stay safe.
Mike Hennessy Sr
Chairman and Founder
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From the Editor

Public Mistrust May Undermine HPV and COVID-19 Vaccines

By MAURIE MARKMAN, MD

This should be a time of celebration in the realm of cancer prevention. The FDA recently approved the use of a 9-valent recombinant vaccine for the prevention of oropharyngeal and other head and neck cancers caused by human papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58. This vaccine has previously been approved for delivery in females aged 9 to 45 years to prevent cervical, vulvar, vaginal, and anal cancers caused by HPV, as well as precancerous or dysplastic lesions caused by certain HPV types. Further, the vaccine has been approved for males aged 9 to 45 years to prevent anal cancer and anal intraepithelial neoplasia. This critically important development recognizes the remarkably impressive data demonstrating the value of HPV vaccination of both females and males in the prevention of malignant disease. The future impact of the standard-of-care administration of this remarkably safe and effective cancer prevention vaccine cannot be overstated.

In a 2016 report, the Centers for Disease Control and Prevention noted an average of almost 39,000 HPV-associated cancers occurred in the United States each year from 2008 to 2012 (approximately 23,000 in women and 16,000 in men), with 80% of these cancers directly attributable to HPV infection. Worldwide, there are approximately 600,000 cases of HPV-related cancers, the incidence of which could be substantially reduced through an effective international HPV vaccination strategy.

It should be further noted that although the incidence of cervical cancer has decreased over time due to effective population-based screening, the incidence of HPV-associated anal and oropharyngeal cancers has been increasing, and no effective screening strategies exist for these difficult malignances. Thus, prevention becomes even more critical and clinically relevant. Finally, it is important to realize that the association between HPV high-risk types (predominantly HPV-16) that are present in the 9-valent vaccine and noncervical cancers is even stronger than that found between HPV high-risk types and cervical cancer. For example, in the United States, 60% of oropharyngeal cancers are due to HPV infection and 90% of these infections are caused by HPV-16. Notably, even at this early point following the routine use of HPV vaccination, there is striking evidence of a reduction in the population-based prevalence of HPV-16 and HPV-18. Yet despite these impressive outcomes and favorable policy decisions, these are disquieting times for clear and decisive messaging regarding vaccines, including the HPV cancer prevention vaccination strategy.

Anti-vaccination influence grows

It is increasingly evident that the anti-vaccination movement in the United States and worldwide is gaining strength and a larger audience. As noted in a recent highly provocative analysis of 3 billion Facebook users, investigators found that although overall there were more “followers” of pro-vaccination pages, the anti-vaccination pages were far greater in number. Further, and of perhaps greatest concern, the followers of the anti-vaccination pages appeared to have greater overlap with “undecided individuals” than the followers of the material provided by pro-vaccination groups. The investigators stated that their “theoretical framework reproduces the recent explosive growth in anti-vaccination views and predicts that these views will dominate in a decade.” This is indeed a stunningly scary conclusion.

As noted in a recent commentary, while the pro-vaccination groups highlight the straightforward argument that currently available standard-of-care vaccines are both safe and effective, anti-vaccination messages include issues unrelated to the objective benefits of this major public health advance such as concepts of personal freedom and multiple conspiracy theories. Against this backdrop, we turn to the current highly public debate regarding the development of a vaccine strategy for the coronavirus 2019 (COVID-19). The quite understandable urgency to find and implement an effective vaccine approach to prevent serious illness associated with this novel virus has led to an uncoordinated scientific,
industry, and governmental response to this complex process. Claims that a safe and effective vaccine will be available at the end of this calendar year or early next year have been challenged by many who have extensive experience in the development of currently available childhood and adult vaccine products.

Appropriately noted was the example of the very rapid deployment of the Salk polio vaccine and the terrible production error in 1955 that resulted in 40,000 children developing polio directly and the start of another outbreak, causing 10 deaths and leading to permanent crippling in another 164 individuals.9

Further, in the rush to create commercial vaccines to immunize the public against COVID-19, there are reports that the populations most at risk of experiencing a serious outcome, the elderly and individuals with comorbid medical conditions, may either be excluded from some existing and planned clinical trials or underrepresented in the study populations.10 One must ask: What is the point of developing a vaccine that has not been demonstrated to be safe and effective in the group of patients most in need of protection?

And, what will happen if in this sprint to develop a COVID-19 vaccine, one or several products approved for routine commercial use are revealed to cause a small but clearly observable risk of serious adverse events that are unfortunately not recognized during the preclinical and clinical research phase, the time when such events should be recognized if they occur? What will happen to societal faith in science and those responsible for establishing public health policy?

If this distressing scenario becomes reality, what will happen to critical efforts to strongly encourage the well-established safe and effective vaccination for childhood and adult illnesses, including strategies to prevent thousands of HPV-related cancers? It does not take much thinking or imagination to know the answer to this disturbing question.

REFERENCES

**FDA DIGEST**

**Selinexor Gains Approval for DLBCL**

Selinexor (Xpovio) is now indicated for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, who received 2 or more prior therapies.

The approval is based on findings from the phase 2b SADAL study (NCT02227251), which demonstrated a 29% overall response rate (ORR), including an 13% complete response rate in 134 patients with relapsed or refractory DLBCL treated with the oral selective inhibitor of exportin 1.

To be eligible to participate, patients had to have received at least 2 but no more than 5 prior systemic regimens for the treatment of DLBCL. Of the 39 patients who achieved a partial or complete response, 38% maintained a response at 6 months and 15% had a response at 12 months. The median time to first response was 8.1 weeks (range, 6.7–16.4).

Selinexor was previously approved in combination with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

**TO READ MORE, VISIT** [bit.ly/3IGz9w](bit.ly/3IGz9w)

**First Therapy Arrives To Address TIO**

Burosumab-twza (Crysvita) is the first FDA-approved therapy for tumor-induced osteomalacia (TIO), a rare disease characterized by tumors that cause weakened and softened bones. The agent can now be administered to patients 2 years and older.

The decision is based on safety and efficacy data from 2 studies that cumulatively enrolled 27 patients with TIO, each of whom received burosumab-twza every 4 weeks. In the first study, half the participants achieved normal phosphate levels through week 24 and retained normal or near-normal phosphate levels through week 144. Bone scan results suggested healing of osteomalacia-related bone lesions. Data from the second study showed that 69% of patients achieved normal phosphate levels through week 24 and retained normal or near-normal phosphate levels through week 88.

TIO-associated tumors release a peptide hormone–like substance known as fibroblast growth factor 23, which controls phosphate levels that play a pivotal role in bone maintenance, cellular energy production, and nerve functionality.

**TO READ MORE, VISIT** [bit.ly/2APOyFE](bit.ly/2APOyFE)

**Tazemetostat Enters Pretreated Follicular Lymphoma Paradigm**

Tazemetostat (Tazverik) can now be administered to adults with relapsed or refractory follicular lymphoma whose tumors are EZH2 positive, as detected by an FDA-approved test, and who received at least 2 prior systemic therapies. The EZH2 inhibitor’s accelerated approval also covers adults with relapsed or refractory disease who have no satisfactory alternative treatment options.

The regulatory decision is based on updated data from an ongoing phase 2 study (NCT01897571) demonstrating a 69% and 35% objective response rate in patients with EZH2-mutant disease and wild-type EZH2 follicular lymphoma, respectively. The complete response rate was 13% in patients with EZH2 mutations and 4% in patients with wild-type disease. Findings indicated that the partial response rate was also higher in patients with EZH2-mutant follicular lymphoma (56% vs 39%).

The study enrolled 45 patients with EZH2 activating mutations and 54 with wild-type EZH2 disease who received 2 or more prior lines of systemic therapy. Tazemetostat was administered at 800 mg twice daily.

An international, adaptive phase 3 trial (NCT04224493) will evaluate tazemetostat combined with lenalidomide (Revlimid) and rituximab (Rituxan) in approximately 500 patients with follicular lymphoma in the second- or later-line setting. The study will be used to support the full approval of tazemetostat in follicular lymphoma and has already begun its safety run-in stage.

**TO READ MORE, VISIT** [bit.ly/3dkJynS](bit.ly/3dkJynS)

**Pembrolizumab Adds a New Indication in cSCC**

The portfolio of available treatment options for recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation expands with the addition of pembrolizumab (Keytruda).

The anti–PD-1 agent’s approval is based on efficacy data from the phase 2 KEYNOTE-629 study (NCT03284424), which demonstrated an objective response rate of 34% (95% CI, 24%-44%) in adults with recurrent or metastatic cSCC or locally advanced, unresectable cSCC that is not amenable to surgery, radiation, and/or systemic therapies. The median duration of response was not reached (range, 2.7–13.1+ months).

The objective response rate and response duration end points were measured per blinded independent central review in accordance with RECIST 1.1 criteria, which were modified to follow a total of 10 target lesions and a maximum of 5 target lesions per organ. KEYNOTE-629 participants received single-agent pembrolizumab at 200 mg every 3 weeks until progressive disease, unacceptable toxicity, or completion of the maximum treatment time, which was 24 months.

**TO READ MORE, VISIT** [bit.ly/2NFCOX3](bit.ly/2NFCOX3)

**Gemtuzumab Ozogamicin Gets Green Light for Pediatric Patients With AML**

The indication for gemtuzumab ozogamicin (Mylotarg) for newly diagnosed CD33-positive acute myeloid leukemia (AML) now includes pediatric patients 1 month and older.

The decision to broaden the antibody-drug conjugate’s indication in this setting is based on data from the phase 3 AAML0531 study (NCT00372593), which demonstrated an event-free survival hazard ratio of 0.85 (95% CI, 0.71-0.99). The estimated percentage of patients free of induction failure, relapse, or death at 5 years was 48% (95% CI, 43%-52%) in the gemtuzumab ozogamicin group compared with 40% (95% CI, 36%-45%) in the chemotherapy group. There was no difference in overall survival between the 2 treatment arms.

AAML00531 enrolled 1063 patients 1 month or older with newly diagnosed AML. The participants were randomized to 5 cycles of chemotherapy alone or in combination with 3 mg/m² of gemtuzumab ozogamicin, administered once on day 6 in induction 1 and once on day 7 in intensification 2.

**TO READ MORE, VISIT** [bit.ly/2BhuERN](bit.ly/2BhuERN)

**Indication for Gardasil 9 Vaccine Expands**

Gardasil 9 received an accelerated approval for oropharyngeal cancer and other head and neck malignancies caused by human papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58, expanding the patient population that is eligible for the HPV 9-valent recombinant vaccine. Gardasil 9’s latest indication is based on its effectiveness in preventing HPV-associated anogenital disease, according to Merck, the vaccine’s developer.
Gardasil 9 was previously indicated for use in females between ages 9 and 45 to prevent cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58, as well as genital warts caused by HPV types 6 and 11. The vaccine also had been approved for precancerous or dysplastic lesions caused by these HPV types, including grades 1 through 3 cervical intraepithelial neoplasia and cervical adenocarcinoma in situ, grade 2 or 3 vulvar intraepithelial neoplasia, grade 2 or 3 vaginal intraepithelial neoplasia, and grades 1 through 3 anal intraepithelial neoplasia.

In males aged 9 through 45 years, Gardasil 9 was indicated for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58, as well as genital warts caused by HPV types 6 and 11, and grades 1 through 3 anal intraepithelial neoplasia.

Gardasil 9’s latest approval will be contingent on the verification of clinical benefit as demonstrated in a confirmatory trial that is underway, Merck said.

TO READ MORE, VISIT bit.ly/3deNExI

Fourth Pegfilgrastim Biosimilar Hits Market
The FDA approved pegfilgrastim-apgf (Nyvepria), a pegfilgrastim (Neulasta) biosimilar, to reduce occurrences of infection manifested by febrile neutropenia in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer agents associated with a clinically significant incidence of the complication.

Pegfilgrastim-apgf’s approval is based on a comprehensive data package with evidence demonstrating a high degree of similarity to the biosimilar’s reference product, according to Pfizer, the biologic’s developer. The recommended dose of the biosimilar is 6 mg administered subcutaneously once per chemotherapy cycle. Notably, pegfilgrastim-apgf is contraindicated in patients with a history of serious allergic reactions to granulocyte colony-stimulating factor agents, including pegfilgrastim or pegfilgrastim products.

Pegfilgrastim-jmdb (Fulphila), the first pegfilgrastim biosimilar to gain FDA approval, was indicated in June 2018 for the same patient population. Pegfilgrastim-cbqv (Udenyca) and pegfilgrastim-bmex (Ziextenzo) were subsequently approved in 2018 and 2019, respectively.

TO READ MORE, VISIT bit.ly/2Yb4x84

FDA Lifts Hold on TELLOMAK Trial in T-Cell Lymphomas
The FDA removed its partial hold on the phase 2 TELLOMAK trial (NCT03902184) of lacutamab (IPH4102) in patients with advanced T-cell lymphoma, according to an announcement from the drug’s developer, Innate Pharma SA.

The dismissal of the hold is based on a quality assessment of a good manufacturing practice (GMP)–certified batch of the investigational agent that was successfully manufactured for lacutamab’s clinical development program, which includes TELLOMAK. With the GMP-approved batch now available, Innate Pharma SA can resume recruiting patients for the TELLOMAK trial in the United States. TELLOMAK is enrolling 250 patients with relapsed or refractory Sézary syndrome and mycosis fungoides who previously received at least 2 systemic therapies.

In January 2020, the FDA placed a partial clinical hold on the TELLOMAK study, suspending enrollment due to GMP deficiencies at Innate Pharma SA’s manufacturing subcontractor site. Authorities in Spain, Italy, and Germany are also being consulted to resume the trial. TELLOMAK investigators are assessing lacutamab both alone combined with chemotherapy in patients with T-cell lymphomas.

TO READ MORE, VISIT bit.ly/2Ve51qC

PER® Transforms Education Programs to Live, Virtual Events
WHEN THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic started to affect live medical meetings in early March, traditional continuing medical education (CME) programming faced a dilemma: reschedule meetings essential to oncology care providers or offer these programs virtually.

Physicians’ Education Resource® (PER®), LLC made the leap to virtual offerings, switching its in-person meetings to live, interactive conferences and adding successful new programs specifically on COVID-19.

Early on in the pandemic, PER® and its parent company MJH Life Sciences, the largest privately held, independent, full-service medical media company in North America, moved quickly to bring oncologists the most up-to-date information on treating patients with cancer during the pandemic. PER® started hosting webinars focused on COVID-19 and has now launched a series, “COVID-19 and Cancer Care: What Oncologists Need to Know Today.” The first live CME-certified COVID-19 webinar that aired on March 23 drew a virtual audience of more than 1200 attendees, who tuned in to hear oncology experts discuss the risk and potential impact of COVID-19 for patients with hematologic and solid tumor malignancies, optimal preventive protocols for how oncologists could protect themselves and their staff across inpatient and outpatient settings, and therapeutic strategies.

“We saw COVID quickly becoming a crisis, and we knew from talking with the community that clinicians didn’t know what to do when treating [patients with] cancer during a time of COVID,” said Phil Talamo, CHCP, president of PER®. “Within a 4-day lead time, we put together a free-flowing virtual webinar where we had experts come together and share best practices and answer questions with the community, which is really the spirit of what CME programming is.”

The “COVID-19 and Cancer Care” program has evolved into an ongoing series of live meetings every Monday, with approximately 500 participants each week. The series features insights from eminent oncologists such as Ruben A. Mesa, MD, director of the University of Texas Health San Antonio MD Anderson Cancer Center; Hope S. Rugo, MD, FASCO, professor of medicine and director of Breast Oncology and Clinical Trials Education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center; Heather A. Wakelee, MD, professor of medicine (oncology) at Stanford University Medical Center in California; and Toni K. Choueiri, MD, director of the Lank...
Center for Genitourinary Oncology and the Kidney Cancer Center at Dana-Farber Cancer Institute in Boston, Massachusetts. The lineup has also featured renowned hematologist Andre H. Goy, MD, physician in chief of Hackensack Meridian Health Oncology Care Transformation Service, chairman & chief physician officer at John Theurer Cancer Center, the Lydia Pfund Chair for Lymphoma, and academic chairman of oncology at Hackensack Meridian School of Medicine at Seton Hall University, all in New Jersey, and a professor of medicine at Georgetown University in Washington, DC.

Beyond COVID-19-focused online CME activities and webinars, the transition of various live events and conferences from an in-person to a digital format has been a driving force at PER®. One innovation is the ASCO Direct Highlights® series featuring expert analysis of clinical findings presented during the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. These sessions aired live during June and are available on PER®’s website to registered participants. PER® also quickly transformed its multiday in-person conferences to a virtual format. Just 1 day before the 13th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies conference was scheduled to take place on March 13, New York Gov. Andrew M. Cuomo formally banned all public gatherings of more than 500 people. MJH Life Sciences™, however, had already made the decision days before to pivot and present the conference as a virtual meeting.

The upcoming 19th Annual International Congress on the Future of Breast Cancer® East, July 17 to July 18, and 19th Annual International Congress on the Future of Breast Cancer® West, July 31 through August 1, will be presented as live webcasts. The 21st Annual International Lung Cancer Congress® will also take place as a live webcast from July 23 to July 25.

According to Talamo, it is very difficult to mirror an in-person program. Clinicians come to events not only to stay up to date on the content but also to interact with the experts and ask them questions. “The biggest opportunity we had, which was also the biggest challenge, was how to create highly interactive programs where there can be Q&A [sessions], where attendees can interact with the faculty in real time, and where faculty can poll the audience and comment on what their results are in real time. These are the components that really foster that interaction with a capital ‘I,’” he said. “And it is something that attendees have come to expect from a first-class PER® educational session.”

But Talamo and his team at PER® rose to the meet the challenge, converting 100% of the programing that was scheduled from in-person events to virtual events from March 2020. Additionally, the company has seen many repeat attendees. Feedback from the events indicates that the programing is engaging and interactive, and attendees like the ability to be able to ask questions.

Participation in the virtual meetings mirrors that of the in-person events. Attendees come for the content and the faculty, Talamo said. “The programs that do well live and in person also do well online. For virtual programming, we have been designing them to be content-relevant based on timeliness. Depending on the data cycle, the format may change. We’ve done a number of post-ASCO webcasts and depending on the ASCO data [that we are presenting], we’re going to have varying methods of disseminating [information], with both traditional lectures that provide detailed analyses of new studies and also panel discussions such as Medical Crossfire® to address diverse perspectives of data interpretation.”

Despite the disruption caused by the COVID-19 pandemic, PER® has continued its mission to keep community oncology care providers informed and connected with experts in the field. “We fulfilled our commitment to the community to make sure that education was available. We have proven that we can continue to be the trusted provider and resource in education through both virtual and on-demand activities. So even if this [pandemic] continues into next year, our incredible team has done a very nice job of keeping the community armed with the data they need and the expertise to care for their patients,” Talamo said.

Although Talamo is unsure when live events will resume, he expects that when they do, there will likely be a live stream or virtual component to all events. Clinicians may still be unable attend because of institution restrictions on travel. These clinicians, however, depend on the data that are provided through these events to treat their patients. There is so much uncertainty about COVID-19, and no one knows what is going to happen next, he noted.

“The one thing we do know is people are still going to get cancer, and they are still going to need state-of-the-art treatment. Things are going to continue to change and evolve. We want to make sure we are doing all we can as a trusted provider of education to support clinicians. The impact of COVID is real, and the spirit of the oncology community is going to lead to a positive path forward,” Talamo concluded.
EXPLORE TIL IMMUNOTHERAPY

TIL MANUFACTURING AT IOVANCE STARTS WITH ISOLATING TUMOR-INFILTRATING LYMPHOCYTES (TIL) from a surgically resected piece of a patient’s tumor. The isolated TIL, which may recognize multiple patient-specific antigens expressed by the tumor, are expanded to billions of cells. Prior to infusion of TIL, the patients are treated with non-myeloablative lymphodepletion preconditioning to remove the suppressive tumor micro-environment. Once the TIL are infused, the patients receive up to 6 doses of IL-2 to support expansion and anti-tumor activity of the TIL.

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YOU OR SOMEONE YOU KNOW MAY QUALIFY FOR ONE OF OUR TIL THERAPY CLINICAL STUDIES IF INITIAL CRITERIA ARE MET:

✓ Diagnosis of:
  • Recurrent, metastatic or persistent cervical cancer
  • HPV + or - recurrent and/or metastatic HNSCC
  • Unresectable or metastatic melanoma, stage IIIIC or IV
  • Locally advanced or metastatic NSCLC, stage III or IV
✓ At least one resectable tumor for TIL generation
✓ 18 years old or older
✓ ECOG PS 0-1

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Multiple Solid Tumors: NCT03645928
(Melanoma, HNSCC, NSCLC)

YOU OR SOMEONE YOU KNOW MAY QUALIFY FOR ONE OF OUR TIL THERAPY CLINICAL STUDIES IF INITIAL CRITERIA ARE MET:

✓ Diagnosis of:
  • Recurrent, metastatic or persistent cervical cancer
  • HPV + or - recurrent and/or metastatic HNSCC
  • Unresectable or metastatic melanoma, stage IIIIC or IV
  • Locally advanced or metastatic NSCLC, stage III or IV
✓ At least one resectable tumor for TIL generation
✓ 18 years old or older
✓ ECOG PS 0-1

If these key eligibility criteria are met, you may be eligible to participate in our clinical study program. There are additional eligibility criteria that must be met and can only be assessed by a study physician.

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and efficacy of this therapy has not been determined.
New Indication Propels Brigatinib Into the Front Line for ALK-Positive NSCLC

by RACHEL NAROZNIAK, MA

THE TYROSINE KINASE INHIBITOR BRIGATINIB (Alunbrig) holds the promise of superior outcomes compared with standard-of-care option crizotinib (Xalkori) in patients with ALK-mutant non–small cell lung cancer (NSCLC).

On May 22, 2020, the FDA approved brigatinib for the frontline treatment of patients with ALK-positive metastatic NSCLC, as detected by an FDA-approved test. Brigatinib was initially approved in 2017 for patients with ALK-positive disease who either experienced disease progression on crizotinib or were unable to tolerate the agent.1,2

Brigatinib’s latest approval is based on progression-free survival data from the phase 3 ALTA-1L trial (NCT02737501) that demonstrated frontline treatment with brigatinib led to a median progression-free survival of 24 months (95% CI, 18.5—not estimable) versus 11 months (95% CI, 9.2-12.9) with crizotinib (HR, 0.49; 95% CI, 0.35-0.68; P<.0001). The confirmed overall response rates were 74% (95% CI, 66-81) and 62% (95% CI, 53-70), respectively.1

A subset of the clinical samples collected from ALTA-1L were retrospectively tested with the Vysis ALK Break Apart FISH Probe Kit, which was approved in tandem with brigatinib as a companion diagnostic to help select patients eligible to receive the drug. Of the 270 patients enrolled, 239 had positive results.

In an interview with OncologyLive®, Thomas E. Stinchcombe, MD, an expert in lung cancer at the Duke Cancer Institute and professor of medicine at Duke University School of Medicine, both in Durham, North Carolina, discussed brigatinib’s mechanism as well as the next steps to advance the treatment paradigm for patients with ALK-positive NSCLC.

Q What was noteworthy about the efficacy data that led to the approval?

The progression-free survival was significantly longer with brigatinib compared with the standard therapy, crizotinib. The difference was particularly striking when we looked at the patients with brain metastasis at baseline. Brigatinib continued to be of benefit in patients without brain metastasis as the ALTA-1L trial progressed.

Q What toxicities do clinicians need to be aware of?

I would break down the toxicities to 3 broad categories. One is laboratory-associated adverse events such as increased amylase lipase, increased creatinine, and increased creatine phosphokinase. These need to be monitored without regular laboratory evaluation. Investigators also noted an increase in hypertension; about 10% of patients had grade 3 hypertension.

The toxicity that I think is unique to this drug and probably requires the closest observation is the rate of interstitial lung disease/pneumonitis. In the brigatinib arm, about 5% of patients had interstitial lung disease/pneumonitis versus 2% in the crizotinib arm. This drug has a unique sort of early-onset pulmonary events, defined in this trial as events that occur within the first 14 days. These were observed in about 3% of patients in the brigatinib arm and none in the crizotinib arm.

Q Mechanistically, what causes brigatinib to be more efficacious than crizotinib in patients with brain metastases?

With crizotinib, we found that some patients with this disease would develop ALK tyrosine kinase resistance mutations, which was a common mechanism for resistance. Additionally, we saw that crizotinib penetrated the blood-brain barrier poorly, so a brain metastasis or central nervous system disease often was a site of disease progression.

Brigatinib targets a broad range of those ALK resistance mutations and has better central nervous system penetration than crizotinib; thus, it delays the development of resistance and has better central nervous system activity.

Q How does this agent advance the NSCLC paradigm, and what are the next steps?

Among patients with adenocarcinoma, depending on the case series of patients, anywhere from 5% to 10% will have an ALK rearrangement. This is a very exciting space. We had the initial approval [of] crizotinib, and then more recently, alectinib [Alecensa] has been approved in the frontline setting. The next-generation ALK inhibitors have improved the outcomes of patients by prolonging progression-free survival by several years. We’re looking to make further improvements and have additional treatment options for this patient population.

The inevitable comparison to brigatinib is going to be the current standard, alectinib. If you do the cross-trial comparisons, the efficacy looks relatively similar, so I think most physicians are going to talk to their patients about alectinib and brigatinib and the relative benefits and the toxicity associated with each of them.

Regarding next steps, we have moved our next-generation agents into the frontline setting, but we need to develop drugs that are active after first-line treatment with next-generation ALK tyrosine kinase inhibitors. The field also needs a better way of defining who benefits from specific ALK inhibitors, potentially by using ALK mutation status, so we can continue to make progress in this disease. Current trials will investigate the optimal sequence of ALK tyrosine kinase inhibitors.

REFERENCES
PIVOTAL CLINICAL TRIAL

ALTA-1L (NCT02737501), a multicenter trial that enrolled 275 patients with advanced ALK-positive NSCLC who had not previously been treated with an ALK-targeted therapy. Patients were permitted to have received 1 prior regimen of chemotherapy in the locally advanced or metastatic setting. Neurologically stable patients with treated or untreated central nervous system metastases were eligible to enroll; individuals with a history of interstitial lung disease (ILD), drug-related pneumonitis, or radiation pneumonitis were excluded.

BASELINE PATIENT CHARACTERISTICS

Efficacy population: (N = 275)

- Median age (range): 59 yrs (27-89)
- Smoking history (%): 58% never smoked
- Site of metastases (%):
  - Bone: 31
  - Liver: 20
  - CNS: 35
- ECOG performance status (%): 5/6

41 patients had measurable CNS lesions

FDA approval—May 22, 2020

FDA grants approval for the tyrosine kinase inhibitor (TKI) brigatinib (Alunbrig) for adults with ALK-positive metastatic non–small cell lung cancer (NSCLC) as detected by an FDA-approved test.

Mechanism of action:
- Brigatinib is a TKI with in vitro activity at clinically achievable concentrations (≤ 500 nM) against ALK, ROS1, IGF-1R, and FLT-3 kinases, and EGFR deletion and point mutations, as well as inhibitory effects on cells expressing EML4-ALK fusion proteins and 17 mutant forms associated with resistance to ALK inhibitors.
- The drug has demonstrated in vivo antitumor activity against 4 mutant forms of EML4-ALK.

How supplied:
- 30-, 90-, and 180-mg tablets

Efficacy results in the ALTA-1L trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Brigatinib (n = 137)</th>
<th>Crizotinib (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>24.0 (18.5-NE)</td>
<td>11.0 (9.2-12.9)</td>
</tr>
<tr>
<td>HR (95% CI; P value)</td>
<td>0.49 (0.35-0.68; P &lt; .0001)</td>
<td></td>
</tr>
<tr>
<td>Confirmed overall response rate (95% CI)</td>
<td>74% (66%-81%)</td>
<td>62% (53%-70%)</td>
</tr>
<tr>
<td>P value</td>
<td>.0342</td>
<td></td>
</tr>
<tr>
<td>Complete response (95% CI)</td>
<td>15% (9%-22%)</td>
<td>9% (5%-15%)</td>
</tr>
<tr>
<td>Partial response (95% CI)</td>
<td>59% (50%-67%)</td>
<td>53% (44%-61%)</td>
</tr>
<tr>
<td>Median duration of response, months (95% CI)</td>
<td>NR (19.4-NE)</td>
<td>13.8 (9.3-20.8)</td>
</tr>
<tr>
<td>Responses lasting ≥ 24 months</td>
<td>5%</td>
<td>30%</td>
</tr>
</tbody>
</table>

NE, not estimable; NR, not reached; PFS, progression-free survival.

WARNINGS AND PRECAUTIONS

-ILD/pneumonitis
-Hypertension
-Bradycardia
-Visual disturbance

- Creative phosphokinase elevation
- Pancreatic enzymes elevation
- Hyperglycemia
- Embryo-fetal toxicity

Commonly reported adverse events in the ALTA-1L trial

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Brigatinib (n = 136)</th>
<th>Crizotinib (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Rash</td>
<td>40%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Cough</td>
<td>35%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32%</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>28%</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>25%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

REFERENCE

Ramucirumab Combination Expands Lung Cancer Options

IN NON–SMALL CELL LUNG CANCER (NSCLC), the choices for frontline treatment are swiftly growing. The landscape now includes ramucirumab (Cyramza) in combination with erlotinib (Tarceva).

On May 29, 2020, the FDA approved ramucirumab plus erlotinib for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions (Ex19del) or exon 21 (L858R) mutations. Ramucirumab previously was approved in combination with docetaxel for patients with metastatic NSCLC with disease progression after prior therapy.

The approval is based on efficacy data from the phase 3 RELAY study (NCT02411448) which demonstrated progression-free survival (PFS) benefit with the dual-drug approach. The study enrolled 449 patients with untreated metastatic NSCLC whose tumors harbored EGFR Ex19del or exon 21 (L858R) substitution mutations.

In an interview with OncologyLive®, Edgardo Santos, MD, a clinical affiliate associate professor at Charles E. Schmidt College of Medicine at Florida Atlantic University in Boca Raton, Florida, and a medical oncologist at Florida Precision Oncology, a Division of 21st Century Oncology, in Aventura, Florida, discussed the unprecedented PFS in patients with EGFR mutations.

Q What is noteworthy about the efficacy data that led to this approval?

The RELAY study is no different from most of the other studies of EGFR [tyrosine kinase inhibitors] TKIs in patients with EGFR-mutant NSCLC that have been conducted since 2008: all had a primary end point of PFS. The RELAY study met its primary end point and the FDA approved ramucirumab and erlotinib as a frontline therapy for patients with NSCLC who have EGFR exon 19 or exon 21 mutations based on the combination’s superior PFS compared with the comparator group using erlotinib alone.

In the history of EGFR TKI development, regardless of the TKIs that we have used in the past, including gefitinib [Iressa], erlotinib, afatinib [Gilotrif], dacomitinib [Vizimpro], and even osimertinib [Tagrisso], patients with the exon 21 abnormality have been less sensitive to TKIs and therefore, their PFS has been lower than those with exon 19 deletions. For example, in the FLAURA study [NCT03521154] of upfront osimertinib, the PFS in this group was 14.4 months compared with 21.4 months for patients with an exon 19 deletion.

However, in RELAY the PFS in patients with exon 21 deletions was 19.4 months. We have never seen that kind of PFS in this particular group.

Q How does this regimen affect the use of TKIs available for treating this disease?

By National Comprehensive Cancer Network [NCCN] data, therapy for patients with EGFR-mutant lung cancer is saturated with TKIs. We have first-generation TKIs such as gefitinib and erlotinib, second-generation TKIs including afatinib and dacomitinib, and third-generation inhibitors like osimertinib. These are all classified as category 1 treatments by the NCCN. Of them, osimertinib has been chosen as the preferred agent because it had the longest PFS reported of all the single-agent TKIs, which was 18.4 months. Recently, reported data from the FLAURA study [NCT02296125] showed an overall survival [OS] benefit favoring osimertinib over gefitinib or erlotinib, with a median OS of 38.4 months versus 31.8 months.

Erlotinib in combination with ramucirumab is classified as a category 2A recommendation by the NCCN because of the unprecedented PFS of 19.4 months that was seen with this doublet therapy. Overall survival data from RELAY are immature.

Q Please describe the doublet therapy’s safety profile.

There have not been any red flags in terms of toxicities that we have not seen with either agent alone, meaning that the safety data are consistent with what we have seen to date with both agents, not only in lung cancer but also in other tumor types. Ramucirumab is an antiangiogenic agent that has FDA approval in several other tumor types. The toxicity profiles of both agents are very well known.

In the RELAY study, some toxicities that we are accustomed to seeing occurred a little more frequently; however, most of the toxicities in the trial were grade 1 and grade 2, so the adverse events were very mild and easy to handle. We saw hypertension, which is very classic of antiangiogenic agents like ramucirumab, as well as proteinuria; rash was also seen at [a] higher incidence with the combination than when we use erlotinib alone. In RELAY, the incidence of hypertension was higher than in other trials where ramucirumab has been studied.

Q What causes these agents to have synergy?

In the past, several preclinical studies have shown that dual blockade of the EGFR and VEGF pathways is synergistic. The antitumor activity is higher when compared with inhibition of the EGFR pathway alone. We also know that when tumor cells harbor EGFR mutations, VEGF is upregulated in the tumor microenvironment, so we know that dual blockade makes sense in this instance.

Q What are the next steps for this combination?

We are waiting for the OS data from the RELAY study, which are immature at the time of publication. We will wait for this data to see how much the addition of ramucirumab to erlotinib improved the OS that we have seen so far with osimertinib monotherapy.

Ramucirumab is also being studied in combination with osimertinib, so we are eagerly awaiting these efficacy results.

Also, the addition of ramucirumab to erlotinib did not affect the incidence of EGFR T790M mutation, a genomic abnormality which confers resistance to first- and second-generation TKIs, leaving the door open to use osimertinib as a salvage therapy in this scenario.

To hear more from Edgardo Santos, MD, listen to our FDA Approval Insights podcast.

LISTEN NOW bit.ly/301WsmS
FDA approval—May 29, 2020
FDA grants approval for ramucirumab (Cymzantma) in combination with erlotinib (Tarceva) for the first-line treatment of metastatic non–small cell lung cancer (NSCLC) with EGFR exon 19 deletions (Ex19del) or exon 21 (L858R) mutations.

Use an FDA-approved companion diagnostic to select patients for therapy.

Mechanism of action:
- Ramucirumab is a VEGFR2 antagonist that specifically binds VEGFR2 and blocks binding of the VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D.
- The agent inhibits ligand-stimulated activation of VEGFR2 to obstruct ligand-induced proliferation and migration of human endothelial cells.
- Ramucirumab inhibited angiogenesis in an in vivo animal model.
- Erlotinib reversibly inhibits the kinase activity of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, inhibiting downstream signaling.
- Erlotinib's binding affinity for EGFR Ex19del or exon 21 (L858R) mutations is higher than its affinity for the wild-type receptor.

How supplied:
- Ramucirumab: One 100 mg/10 mL or 500 mg/50 mL single-dose vial
- Erlotinib: 25-, 100-, or 150-mg tablets

Dosing:
- Ramucirumab: 10 mg/kg administered intravenously over 60 minutes on day 1 of a 21-day cycle prior to docetaxel
- If the first ramucirumab injection is tolerated, all subsequent infusions may be administered over 30 minutes.
- Erlotinib: 150 mg taken on an empty stomach at least 1 hour before or 2 hours after food

Companies:
- Ramucirumab: Eli Lilly and Company
- Erlotinib: Genentech; Astellas Pharma, Inc

PIVOTAL EFFICACY DATA FOR APPROVAL
RELAY (NCT02411448), a multicenter, placebo-controlled trial that enrolled 449 patients with metastatic NSCLC whose tumors harbored EGFR Ex19del or exon 21 substitution mutations. To be eligible to participate, patients must have had measurable disease, no central nervous system metastases, and no known EGFR T790M mutations at baseline.

Efficacy results for approval in the Relay trial

Outcome | Ramucirumab + erlotinib (n = 224) | Erlotinib + placebo (n = 225)
--- | --- | ---
Number of PFS events | 55% | 70%
Median PFS, months (95% CI) | 19.4 (15.4-21.6) | 12.4 (11.0-13.5)
Hazard ratio (95% CI) | 0.59 (0.46-0.76) | <.0001
Stratified log-rank P-value | --- | ---

PFS, progression-free survival.

Select warnings and precautions

<table>
<thead>
<tr>
<th>Ramucirumab</th>
<th>Erlotinib</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Interstitial lung disease</td>
<td>Gastrointestinal perforations</td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>Renal failure</td>
<td>Embryo-fetal toxicity</td>
</tr>
<tr>
<td>Arterial thromboembolic events</td>
<td>Bullous and exfoliative skin disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Cerebrovascular accident</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>Microangiopathic hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Worsening of preexisting hepatic impairment</td>
<td>Ocular disorders</td>
<td></td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome</td>
<td>Hemorrhage in patients taking warfarin</td>
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</tr>
</tbody>
</table>

Commonly reported adverse events in the Relay study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ramucirumab + erlotinib (n = 221)</th>
<th>Erlotinib + placebo (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade ≥3</td>
<td>All grades</td>
</tr>
<tr>
<td>Infections</td>
<td>81%</td>
<td>17%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70%</td>
<td>7%</td>
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<tr>
<td>Hypertension</td>
<td>45%</td>
<td>24%</td>
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<tr>
<td>Stomatitis</td>
<td>42%</td>
<td>2%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>34%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Median age (IQR)</th>
<th>Smoking status</th>
<th>Pathological diagnosis at study entry (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 years (57-71)</td>
<td>Never smoked</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>64 years (56-70)</td>
<td>Reported ever smoking</td>
<td>NSCLC not otherwise specified</td>
</tr>
</tbody>
</table>

EGFR testing method (%)

<table>
<thead>
<tr>
<th>Ramucirumab + erlotinib (n = 224)</th>
<th>Erlotinib + placebo (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therascreen or cobas</td>
<td>57</td>
</tr>
<tr>
<td>Other PCR and sequencing-based methods</td>
<td>43</td>
</tr>
</tbody>
</table>

References

**POLYCYTHEMIA VERA**

**Severity, impact, and implications of symptom burden in PV**

*Patients with polycythemia vera (PV) experience a unique constellation of troublesome symptoms.*\(^1\) These can vary in intensity and/or emerge throughout the course of PV, including in patients whose disease is well controlled by other measures.\(^1\)-\(^4\) However, consistently monitoring symptoms and therapy may help patients with PV achieve their individual quality of life (QoL) goals.

PV is a myeloproliferative neoplasm (MPN) characterized by abnormal proliferation of mature myeloid cells. Symptom burden in PV and other MPNs may also be severe, similar to that seen in acute myeloid leukemia, non-Hodgkin lymphoma, or metastatic cancer.\(^5\),\(^6\) Patients with PV are also at risk for thrombotic events (up to 40%), and transformation to post-PV myelofibrosis (MF; ~10%) or acute myeloid leukemia (AML; ~3%).\(^7\),\(^8\) Given the prevalence of symptoms and the burden they may impose on patients, symptom alleviation is a major objective in the evaluation of patients with PV.\(^5\),\(^10\)

*Given the prevalence of symptoms and the burden they may impose on patients, symptom alleviation is a major objective in the evaluation of patients with PV.*\(^5\),\(^10\)

Although PV is chronic, symptoms can be dynamic, changing throughout the course of the disease. Given their dynamic nature and potential to reveal aspects of the underlying biology, it is essential to monitor symptoms when PV is diagnosed and regularly as the disease is being managed. The occurrence of a new event such as thrombosis, diabetes diagnosis, or change in medication may affect symptoms. Symptom monitoring can help healthcare professionals (HCPs) interpret how the variety of clinical changes have affected the patient’s disease along with helping to recognize the potentially subtle signs of disease progression.\(^11\)

**Tracking Symptoms in PV**

Surrogates of disease burden such as risk scores and blood cell counts often fail to correlate with symptomatic burden, but validated patient reported outcome (PRO) tools may permit objective and rapid assessment of the symptom burden in patients with PV.\(^5\) To assess the unique spectrum of symptomatology seen in patients with MPNs, we developed the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and the more concise MPN-SAF Total Symptom Score (MPN-SAF TSS), commonly known as the MPN-10.\(^6\),\(^10\),\(^12\) This tool includes the most representative and pertinent MPN-related symptoms – fatigue, vascular symptoms, constitutional symptoms, and spleen-related symptoms.\(^10\),\(^12\) The importance of recognizing symptoms in MPNs and the value of surveys to quantify PROs was substantiated by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms, which incorporated symptom burden assessment as part of routine evaluation of patients with PV in 2017.\(^13\)

*The MPN-10 is designed to assess the unique spectrum of symptomatology seen in patients with MPNs.*\(^12\)

Visit mpnconnect.com/mpn-resources.aspx for the MPN-10 form and additional resources

At our clinic, we provide the MPN-10 to patients during the check-in process. This opens a discussion between patient and HCP. I document the MPN-10 sum score into the patient’s chart and refer to it at future visits. By providing an objective, quantitative PRO, these surveys provide data that facilitate management decisions.

**Evaluating Symptom Burden to Assess the Patient’s Condition**

With these data, we then thoroughly examine the patients for signs of disease such as splenomegaly and ask probing questions to gain a deeper understanding of symptom burden. Despite nearly 90% of patients reporting symptoms at
Patients with polycythemia vera (PV) experience a unique constellation of troublesome symptoms. This is likely because of the nature of symptoms in PV that causes them to not be readily apparent to physicians. At our clinic we have noted that serial assessment of symptom burden using PRO tools allows for direct assessment of the patient experience and has demonstrated in clinical trial settings to be a sensitive clinical indicator of disease progression. Some of the key symptoms I look for are fatigue, abdominal discomfort, early satiety, headaches, bone pain, pruritus, and depression. I also pay close attention to the overall QoL, which can be affected by both the severity and the multitude of symptoms in PV. Older individuals may not report their symptoms, regarding them as a natural sign of aging, or patients may have grown accustomed to the symptoms as they gradually emerged during the long course of PV. The erroneous acceptance of this new, symptomatic “normal” can be corrected by educating patients about PV.

**Incorporating Symptoms into the Clinical Assessment Routine**

Providing individualized care — which encompasses PV disease-related factors, any comorbidities, and the patient’s personal health and wellness goals — is the ultimate goal when I treat patients with PV. Developing a routine to track symptoms and other factors can facilitate this. As physicians, even if we do a thorough job when asking patients with PV about what symptoms they are experiencing, we may easily miss the severity of the symptoms — especially in patients who have a large number of different symptoms. The continuum of disease and patient characteristics combined with the chronic nature of PV emphasizes the need to routinely monitor and track therapy, disease signs, and symptoms. Overall, this can be thought of as reading the patient’s diary of disease to get a complete picture of the impact of PV on both their underlying biology and their lifestyle goals. Patients with PV can live for many years with a severe symptom burden, and trying to optimize QoL is paramount.

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Sr. Director, Medical Affairs at Incyte; Asst. Prof. of Medicine at the University of Texas Health Science Center at San Antonio

This article, sponsored by Incyte Corporation, is based on a paid interview with Robyn M. Scherber, MD, MPH, Sr. Director, Medical Affairs at Incyte, and Asst. Prof. of Medicine at the University of Texas Health Science Center at San Antonio, conducted on May 29, 2018.

**References:**

13. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.2.2019. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed October 29, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
COVID-19 Pandemic Accelerates RWD-Based Initiatives in Oncology

by RACHEL NAROZNIAK, MA

THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic has magnified the value of real-world data (RWD) in oncology. The FDA is presently spearheading several initiatives aimed at refining the role of RWD in cancer care to guide clinical trial development, procure answers to pressing clinical questions, and support regulatory decisions for in vitro diagnostics, according to presentations shared during a major symposium at the 2020 American Association for Cancer Research Virtual Annual Meeting II.

“We now find ourselves in a grand experiment,” said Paul G. Kluetz, MD, deputy director of the Oncology Center of Excellence at the FDA. “By necessity, COVID-19 has pushed the cancer clinical trial community out of its comfort zone to rapidly deploy remote assessments and digital health technology, [prompting] unprecedented collaboration to explore the use of real-world data. We cannot lose this opportunity to learn and advance our knowledge of the strengths and limitations of decentralized trials and real-world data to move our cancer research enterprise to a more efficient and more patient-friendly model.”

Long before COVID-19, Kluetz explained, there were calls in oncology to learn from RWD and “decentralize” standard components of clinical trials in favor of more “patient-friendly” alternatives such as digital health technology to facilitate remote assessments. However, only now has the oncology field so broadly begun to adopt different operational tactics and draw upon RWD to inform management approaches for both COVID-19 and cancer. “We’ve witnessed a great interest in learning from our health care systems and taking advantage of real-world data to rapidly expand our knowledge,” Kluetz said.

With crises come opportunity, and many clinical questions now require answers. For example, can data collected from cancer trials conducted during the COVID-19 pandemic be leveraged to understand the effects of remote assessments and decentralized trial procedures on safety and efficacy outcomes? Also, can RWD be used to characterize the natural history of COVID-19 and its effects on patients with cancer?

The FDA is currently working with data holders, data analysts, and research institutions around the world to develop initiatives that not only address these inquiries but also probe beyond them, to clarify when and how specifically RWD can most optimally be used to improve current methodologies in oncology and inform new ones in the age of COVID-19.

THE COVID-19 EVIDENCE ACCELERATOR

The COVID-19 Evidence Accelerator is a collaborative, RWD-driven initiative spearheaded by the Reagan-Udall Foundation for the FDA in collaboration with Friends of Cancer Research.

The Accelerator brings together the country’s leading experts in health data aggregation and analytics, overlapping them with partners across government agencies to develop an initial set of priority questions regarding the therapeutic interventions, treatment settings, and associated outcomes that would guide early COVID-19–focused data aggregation efforts. Three of the urgent critical inquiries include understanding the epidemiology of COVID-19; the predictors of patients who would be at risk of developing severe manifestations of COVID-19; and the patterns of general outcomes for people with COVID-19, including death and time to disease resolution. The questions have been crowdsourced, curated, and prioritized, so teams across the country can identify the highest priority items, according to Amy P. Abernethy, MD, PhD, principal deputy commissioner and acting chief information officer of the FDA.

In an effort to provide a dual interrogation of the RWD and inform the Oncology Center of Excellence’s COVID-19–related...
research endeavors, the oncology work group was established in June 2020 to develop questions specific to the management of COVID-19 in patients with cancer. Questions included the safety and efficacy of immunotherapy in patients with COVID-19 and lung, melanoma, bladder, and other malignancies, as well as the rates and impact of reduced screening and treatment (FIGURE).1

To structure researchers’ investigative efforts, the Reagan-Udall Foundation for the FDA/Friends of Cancer Research has defined common data elements and translation tables between data models that researchers are encouraged to use. Common protocols for repeated analyses of priority research questions; meetings and forums for rapid cycle feedback and for learning from the insights of participating data partners; and individual accelerator subcommunities dedicated to specific topics, such as therapeutics, diagnostics, and vaccines, have also been established.2 The oncology work group does not limit or divide its investigative focus to 1 of these areas, but rather evaluates each of them.

“The management of a patient with cancer who develops COVID-19 sits across all of the work streams,” Abernethy said. Important considerations for patients with cancer who develop COVID-19 include how therapies perform and what is the difference, if any, in outcomes for a patient with cancer who has had COVID-19 versus one who has not.

These efforts support the widely recognized importance of moving expeditiously to find answers to pressing clinical questions during this unprecedented time in medicine, Abernethy said. “The work of the Evidence Accelerator sits in this larger global data community, where partners across the community understand a critical thing: We need to address the questions of COVID-19 with urgency, and we need to understand the natural history of disease and the effectiveness of potential treatments, and use the information to plan clinical trials,” Abernethy said.1

**SHIELD**

In addition to shaping future oncology clinical trials, leveraging RWD for public health initiatives involving both COVID-19 and cancer is an overarching goal of an initiative known as SHIELD. The Systemic Harmonization and Interoperability Enhancement for Lab Data (SHIELD) project aims to establish interoperability to standardize data sharing among in vitro diagnostic data sources and to illuminate clinical management and understand health outcomes.1,2

“A key problem in leveraging real-world diagnostics is the lack of information on the specific test used and the manufacturer,” said Wendy Rubinstein, MD, PhD, director of Personalized Medicine at the FDA.

“SHIELD is a cross-center and multisite initiative that supports efforts to harness nontraditional in vitro diagnostic data sources while reducing burdens to the health care ecosystem,” Rubinstein explained. Crucial to SHIELD is the development of code mapping manuals to allow for the consistent mapping of the Logical Observations Identifiers Names and Codes (LOINC) that correspond with a given in vitro diagnostic. LOINC is the most widely used coding system for clinical laboratories and electronic health records. For in vitro diagnostics, LOINC codes are used to identify the type of diagnostic used to test a clinical measure.3 SHIELD will “provide a process for consistent definition and use of codes,” thereby supporting interoperability, Rubinstein said.

RWD generated and collected during the COVID-19 pandemic, and thereafter, can also be leveraged to observe change in specific populations. “We realize that physicians are ordering tests on asymptomatic patients and that [test] performance might be different in an exposed population versus in a population of patients who are not exposed,” Rubinstein said.

Time points will also become a key data point and include such queries as: when was immunity established?; how long does it last?; and what is the best way to measure neutralizing antibodies versus other markers of exposure? “These [markers] will set us up to better predict populations establish immunity after a vaccine is available, including among populations of patients with active cancer and not active cancer, hematological

**REFERENCES**


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**FIGURE. Clinical Inquiries For Patients With COVID-19 and Cancer**

- Optimal therapeutic interventions
- Prevalence of thrombosis/coagulopathy, renal failure, and cardiomyopathy in select populations
- The long-term sequelae of COVID-19
- Incidence of multiorgan inflammatory syndrome in pediatric patients
- The impact of reduced screening and delays in diagnosis and adjuvant treatment on mortality
- Best practices and priorities for diagnostic testing

TOP TWEETS

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With the utilization of more targeted recruitment efforts, more high-risk, poor-prognosis African American patients can achieve better representation in research, which can eventually result in more focused treatments @EmilyRencsok @HarvardChanSPH
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Podcast Spotlight

RESEARCH REFLECTIONS
HAMID HOMES IN ON KEY ADVANCES IN MELANOMA RESEARCH
Omid Hamid, MD, director of the Melanoma Center and Phase I Immuno-Oncology Program, and chief of Immunotherapy and Translational Research at The Angeles Clinic and Research Institute in Los Angeles, California, discusses the most noteworthy melanoma data presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program.
LISTEN: bit.ly/2UTOAku

MARVELS IN MEDICINE
GRADISHAR ON THE PERSONAL PURSUIT OF PRECISION MEDICINE IN BREAST CANCER
William J. Gradishar, MD, chief of hematology and oncology in the Department of Medicine at Northwest University Feinberg School of Medicine in Chicago, Illinois, describes his path to oncology research in the field of breast cancer, the experiences that have inspired him throughout his career, and his hope for the continued transition from “shotgun medicine” to precision medicine.
LISTEN: bit.ly/2Yca5PW

FDA APPROVAL INSIGHTS
RAMUCIRUMAB/ERLOTINIB IN EGFR+ METASTATIC NSCLC
Edgardo S. Santos, MD, a medical oncologist at Florida Precision Oncology and a clinical affiliate professor at the Charles E. Schmidt College of Medicine at Florida Atlantic University in Boca Raton, describes the significance of the approval of ramucirumab (Cyramza) in combination with erlotinib (Tarceva) in EGFR-mutant non-small cell lung cancer (NSCLC).
LISTEN: bit.ly/2BSKWRR

TALKING TUMORS
TURNING TO LIQUID BIOPSIES AND IMMUNOTHERAPY IN LUNG CANCER
Kathryn E. Hudson, MD, director of survivorship, and Jeff Yorio, MD, medical oncologist, both of Texas Oncology in Austin, Texas, address best practices for liquid biopsy and immunotherapy use in lung cancer, including the instances in which waiting for testing prior to initiating therapy is appropriate, the accuracy of tumor and liquid biopsies, and optimal sequencing strategies for managing patients with brain metastases.
LISTEN: bit.ly/2YNkMon

ONCLIVE® VIDEOS

RAPID READOUTS:
CHECKMATE 9LA
Martin Reck, MD, PhD, head of the Department of Thoracic Oncology at the Grosshansdorf Lung Clinic in Germany, and lead author of the phase 3 CheckMate 9LA trial (NCT03215706), discusses the rationale for the study and the implications of its findings for patients with non-small cell lung cancer (NSCLC). CheckMate 9LA led to the May 26, 2020 approval of frontline nivolumab (Opdivo) in combination with ipilimumab (Yervoy) and platinum-based chemotherapy in metastatic or recurrent NSCLC.
VIEW VIDEO: bit.ly/2N9XTsl

SHARMAN ON UNMET NEED IN HIGH-RISK R/R CLL
High-risk chronic lymphocytic leukemia (CLL) is defined by the presence of 17p deletions, TP53 mutations, or 11q deletions, and correlates with poor prognoses and inferior progression-free survival rates compared with patients whose disease does not carry these markers. Further study is necessary to yield more effective therapies for this relapsed/refractory (R/R) population, according to Jeff P. Sharman, MD, director of research at Willamette Valley Cancer Institute in Eugene, Oregon, and medical director of hematology research for The US Oncology Network.
VIEW VIDEO: bit.ly/2YbxzVG

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CLAIMS DATA HELP IDENTIFY PATIENTS WITH SEVERE CANCER-RELATED SYMPTOMS

Investigators of a study that sought to establish a claims-based mechanism for identifying patients with metastatic non–small cell lung cancer (mNSCLC) and high levels of patient-reported cancer-related symptoms who could benefit from engagement with health care programs found that claims-based factors associated with severe symptom cluster can enable the selection of these patients. Selecting patients with mNSCLC who are experiencing severe symptoms presents an opportunity for clinicians and other health care stakeholders to improve the health-related quality of life for these patients through outreach programs, and the results of the survey and cluster analysis indicate that the data can be used to direct patients to clinical programs that ameliorate symptoms and improve quality of life.


THE DOWNSTREAM EFFECTS OF the coronavirus disease 2019 on patients with cancer have become apparent over the past few months, said Edward S. Kim, MD. In ASCO Direct Highlights®, a Physicians’ Education Resource® (PER®), LLC virtual program, Kim said that the pandemic has reduced cancer screening and diagnostic testing as well as clinical trials and research. Additionally, there have been fewer visits and referrals, which in turn, led to disruptions in cancer care and a rise in telemedicine. Within clinical practice, Kim said that providers will have to weigh the current standard of care with something that is perhaps less effective but safer for the patient.

Despite these changes, the goals in any individual practice, specifically patient and staff safety as well as adhering to best practices, should remain the same, said Kim.

Kim chairs the Department of Solid Tumor Oncology at Levine Cancer Institute, Atrium Health, in Charlotte, North Carolina,

READ MORE: bit.ly/3871np6

NOTABLE QUOTABLES

“Trastuzumab deruxtecan has been shown to be an active and potent drug for patients with HER2-positive metastatic breast cancer, and it is also active in HER2-amplified colorectal cancer [CRC]...Because of its activity and safety profile, it should be considered as a candidate for CRC...It has not been approved yet, but certainly it is a brilliant candidate.”

—Salvatore Siena, MD
Professor of medical oncology, Universita degli Studi di Milano; director, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Italy

READ MORE: bit.ly/37BeZJg

“There’s a real reason to keep an eye on the data emerging from COSMIC-021 [in solid tumors]. Like a fine wine, the study just keeps getting better and better with more and more interesting data pouring out of it.”

—Sumanta K. Pal, MD
Clinical professor, Department of Medical Oncology & Therapeutics Research; codirector, Kidney Cancer Program, City of Hope

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On June 11, 2020, MJH Life Sciences™ demonstrated its commitment to delivering timely, up-to-date information across the health care spectrum to clinicians with the establishment of Medical World News®. A first-of-its-kind 24-hour news channel for health care professionals, by health care professionals, Medical World News® coalesces content from all brands within the MJH portfolio, including OncLive®, on 1 platform.

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In the final analysis, 1 XOSPATA delivered superior overall survival vs salvage chemotherapy:

- **36%** reduced risk of death with XOSPATA (n=247) vs salvage chemotherapy (n=124)
  - **9.3 months** median OS (95% CI: 7.7, 10.7) vs 5.6 months with salvage chemotherapy (95% CI: 4.7, 7.3)

  \[
  \text{HR}=0.64 \text{ (95\% CI: 0.49, 0.83)}; \ P=0.0004
  \]

The efficacy of XOSPATA was established on the basis of CR\textsuperscript{+}/CRh\textsuperscript{+}, the duration of CR/CRh (DOR), and the rate of conversion to transfusion independence at the first interim analysis:

- **21% CR/CRh** (95% CI: 14.5, 28.8; n=29/138)
  - The median DOR was **4.6 months** with XOSPATA (range: 0.1 to 15.8; n=29/138)

    DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type. Deaths were counted as events

- Among patients in the XOSPATA arm who were transfusion dependent at baseline (n=106), **31.1%** became transfusion independent with XOSPATA during any 56-day post-baseline period (n=33/106)

    Transfusion independence is defined as patients who were dependent on RBC and/or platelet transfusions at baseline and became independent of RBC and platelet transfusions during any 56-day post-baseline period

Gilteritinib (XOSPATA) is the ONLY Category 1 recommendation for patients with relapsed or refractory AML with a FLT3 mutation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\textsuperscript{*}) \textsuperscript{2}

- XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in 371 adult patients with relapsed or refractory FLT3m+ AML\textsuperscript{1,3}

- The efficacy of XOSPATA was based on an interim analysis and a final analysis\textsuperscript{1}:
  - The first interim analysis evaluated the endpoints of CR/CRh, the DOR, and the rate of conversion from transfusion dependence to transfusion independence in 138 patients treated with XOSPATA
  - The final analysis evaluated the endpoint of OS and was measured from the date of randomization until death by any cause

\*FLT3 mutation status: FLT3-ITD, FLT3-TKD, and FLT3-ITD-TKD.\textsuperscript{1}

\textsuperscript{1}The OS endpoint was measured from the date of randomization until death by any cause in the final analysis, which included 371 patients randomized 2:1 to receive XOSPATA or a prespecified salvage chemotherapy regimen.\textsuperscript{1}

\textsuperscript{1}CR defined as normal marrow differential with <5% blasts, ANC $\geq$1.0 x 10\textsuperscript{9}/L and platelets $\geq$100 x 10\textsuperscript{9}/L, no evidence of extramedullary leukemia, and must have been RBC and platelet transfusion independent.\textsuperscript{1}

\textsuperscript{1}CRh defined as marrow blasts <5%, partial hematologic recovery, ANC $\geq$0.5 x 10\textsuperscript{9}/L and platelets $\geq$50 x 10\textsuperscript{9}/L, no evidence of extramedullary leukemia, and could not have been classified as CR.\textsuperscript{1}

\textsuperscript{1}Response was ongoing.\textsuperscript{1}

AML=acute myeloid leukemia; ANC=absolute neutrophil count; CI=confidence interval; CR=complete remission; CRh=complete remission with partial hematologic recovery; FLT3=FMS-like tyrosine kinase 3; HR=hazard ratio; ITD=internal tandem duplication; m+=mutation-positive; NCCN=National Comprehensive Cancer Network; OS=overall survival; RBC=red blood cell; TKD=tyrosine kinase domain.

References: 1. XOSPATA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\textsuperscript{*}) for Acute Myeloid Leukemia V.3.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed 01-29-2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Astellas. XOSPATA. Data on File.

Please see adjacent pages for Brief Summary of Full Prescribing Information, including BOXED WARNING.
Indication
XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

Important Safety Information
Contraindications
XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

WARNING: DIFFERENTIATION SYNDROME
Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

Warnings and Precautions
Differentiation Syndrome (See BOXED WARNING) 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

Posterior Reversible Encephalopathy Syndrome (PRES) 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

Prolonged QT Interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

Pancreatitis 4% of 319 patients treated with XOSPATA in the clinical trials experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

Adverse Reactions
Fetal adverse reactions occurred in 2% of patients receiving XOSPATA. These were cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

7% discontinued XOSPATA treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were asparagine aminotransferase increased (2%) and alanine aminotransferase increased (2%).

The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/ malaise (6%).

Other clinically significant adverse reactions occurring in ≥10% of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities Shifts to grades 3-4 nonhematologic laboratory abnormalities in XOSPATA treated patients included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

Drug Interactions
Combined P-gp and Strong CYP3A Inducers Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases XOSPATA exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

Strong CYP3A inhibitors Concomitant use of XOSPATA with a strong CYP3A inhibitor increases XOSPATA exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor Concomitant use of XOSPATA may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

Specific Populations
Lactation Advise women not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

XOSPATA gilteritinib 40mg tablets
See the full story at XospataHCP.com

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INDICATIONS AND USAGE
XOSPATA® (gilteritinib) is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation based on an FDA-approved test.

DOSAGE AND ADMINISTRATION
Patient Selection
Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage
The recommended starting dose of XOSPATA is 120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response. Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Dose Modification
Assess blood counts and blood chemistries, including creatine phosphokinase, or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response. Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

CONTRAINDICATIONS
XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

WARNINGS AND PRECAUTIONS
Differeation Syndrome
Of 319 patients treated with XOSPATA in the clinical trials, 3% experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, pericardial edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of XOSPATA. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndromes may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

Posterior Reversible Encephalopathy Syndrome (PRES)
Of 319 patients treated with XOSPATA in the clinical trials, 1% experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

Prolonged QT Interval
XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial, 1% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

Pancreatitis
Of 319 patients treated with XOSPATA in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

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

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML treated with gilteritinib 120 mg daily in three clinical trials. The median duration of exposure to XOSPATA was 3.8 months (range 0.1 to 43.4 months).

Fetal adverse reactions occurred in 2% of patients receiving XOSPATA. These included cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%). Of the 319 patients, 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (7%) discontinued XOSPATA treatment permanently due to an adverse reaction.

The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

Overall, for the 319 patients, the most frequent (≥10%) all-grade nonhematological adverse reactions reported in patients were transaminase increased (51%), myalgia/arthritis (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (26%), constipation (26%), eye disorders (25%), headache (24%), diarrhea (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuroapathy (18%), insomnia (15%) and dysgeusia (11%).

The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/malaise (6%).

Shifts to grades 3–4 nonhematologic laboratory abnormalities included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased...
(12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatine kinase increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (9%), hypersensitivity* (8%), pancreatitis* (5%), cardiac failure* (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis* (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

*Grouped terms: cardiac failure (cardiac failure, cardiac failure congestive, cardiomyopathy, cardiomyopathy, chronic left ventricular failure, and ejection fraction decreased), hypersensitivity (anaphylactic reaction, angioedema, dermatitis allergic, drug hypersensitivity, erythema multiforme, hypersensitivity, and urticaria), pancreatitis (amylase increased, lipase increased, pancreatitis, pancreatitis acute), pericarditis/myocarditis (myocarditis, pericardial hemorrhage, pericardial rub, and pericarditis).

**DRUG INTERACTIONS**

**Combined P-gp and Strong CYP3A Inducers**

Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases gilteritinib exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

**Strong CYP3A Inhibitors**

Concomitant use of XOSPATA with a strong CYP3A inhibitor increases gilteritinib exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

**Drugs that Target 5HT2B Receptor or Sigma NonSpecific Receptor**

Concomitant use of gilteritinib may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on findings from animal studies and its mechanism of action, XOSPATA can cause fetal harm when administered to a pregnant woman. There are no available data on XOSPATA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC24) approximately 0.4 times the AUC24 in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

**Data**

**Animal Data**

In an embryo-fetal development study in rats, pregnant animals received oral doses of gilteritinib of 0, 0.3, 3, 10, and 30 mg/kg/day during the period of organogenesis. Maternal findings at 30 mg/kg/day (resulting in exposures approximately 0.4 times the AUC24 in patients receiving the recommended dose) included decreased body weight and food consumption. Administration of gilteritinib at the dose of 30 mg/kg/day also resulted in embryo-fetal death (post implantation loss), decreased fetal body and placental weight, and decreased numbers of ossified sternebrae and cervical and thoracic vertebrae, and increased incidence of fetal gross external (anasarca, local edema, exencephaly, cleft lip, cleft palate, short tail, and umbilical hernia), visceral (microphthalmia, atrial and/or ventricular defects, and malformed/absent kidney, and malpositioned adrenal, and ovary), and skeletal (sternoschisis, absent rib, fused rib, fused cervical arch, misaligned cervical vertebrae, and absent thoracic vertebrae) abnormalities. Single oral administration of [14C] gilteritinib to pregnant rats resulted in transfer of radioactivity to the fetus similar to that observed in maternal plasma on day 14 of gestation. In addition, distribution profiles of radioactivity in most maternal tissues and the fetus on day 18 of gestation were similar to that on day 14 of gestation.

**Lactation**

**Risk Summary**

There are no data on the presence of gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Following administration of radiolabeled gilteritinib to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4 and 24 hours post-dose. In animal studies, gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

**Females and Males of Reproductive Potential**

**Pregnancy testing**

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating XOSPATA treatment.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of XOSPATA.

**Males**

Advise males of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the 319 patients in clinical studies of XOSPATA, 43% were age 65 years or older, and 13% were 75 years or older. No overall differences in effectiveness or safety were observed between patients age 65 years or older and younger patients.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been performed with gilteritinib. Gilteritinib was not mutagenic in a bacterial mutagenesis (Ames) assay and was not clastogenic in a chromsome aberration test assay in Chinese hamster lung cells. Gilteritinib was positive for the induction of micronuclei in mouse bone marrow cells from 65 mg/kg (195 mg/m²) the mild dose tested (approximately 2.5 times the recommended human dose of 120 mg). The effect of XOSPATA on human fertility is unknown. Administration of 10 mg/kg/day gilteritinib in the 4-week study in dogs (12 days of dosing) resulted in degeneration and necrosis of germ cells and spermatid giant cell formation in the testis as well as single cell necrosis of the epididymal duct epithelia of the epididymal head.

**Animal Toxicology and/or Pharmacology**

In the 13-week oral repeated dose toxicity studies in rats and dogs, target organs of toxicity included the eye and kidney.

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MOLECULARLY TARGETED THERAPIES DEMONSTRATED practice-changing results for patients with biomarker-driven lung, colorectal, and ovarian cancers in phase 3 randomized clinical trial findings featured at the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. Data from the 3 noteworthy studies strengthen the rationale for genomic profiling, experts say.

The findings come against a backdrop of the continuing growth of anticancer therapies for patients whose malignancies harbor a genomic aberration. In 2019, 13 of the 38 FDA approvals for oncology indications required testing for a molecular alteration.1 So far this year, 18 of 38 new or expanded approvals for oncology and hematology indications are linked to genetic or protein biomarkers, according to an FDA database search.2

The ASCO 2020 research that is expected to have an impact on the treatment landscape in the 3 malignancies stems from the following studies:

- ADAURA (NCT02511106): Osimertinib (Tagrisso) significantly improved disease-free survival (DFS) compared with placebo as adjuvant therapy for patients with early-stage, EGFR-mutant non–small cell lung cancer (NSCLC) who had undergone complete resection.3 The regimen has the potential to enhance curative outcomes for this population.

- KEYNOTE-177 (NCT02563002): Pembrolizumab (Keytruda) boosted progression-free survival (PFS) compared with standard-of-care chemotherapy as a frontline treatment for patients with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC).4 The FDA approved a new indication for pembrolizumab on June 29, 2020 based on the trial results.5

- SOLO2 (NCT01874353): Olaparib (Lynparza) delivered a 12.9-month median overall survival (OS) benefit compared with placebo as maintenance therapy for patients with BRCA-mutant, platinum-sensitive recurrent ovarian cancer. Investigators said the improvement in this setting is “unprecedented.”

Although clinicians have incorporated the biomarker-driven strategies evaluated in these trials into the treatment landscapes for these malignancies, the findings propel their use into more areas and highlight the clinical utility of molecular profiling, particularly in NSCLC and mCRC. In NSCLC, the ADAURA findings indicate the need for testing before patients reach advanced stages of disease, an approach that current practice does not reflect, Mark G. Kris, MD, a medical oncologist who helped pioneer the molecular characterization of NSCLC, said in an interview with OncologyLive®.

“Every single [patient] who has surgery is going to need a molecular test,” said Kris, the William and Joy Ruane Chair in Thoracic Oncology at Memorial Sloan Kettering Cancer Center in New York, New York. “Up to today, that has not been a standard of care, and in the course of doing that, we’re going to find patients with EGFR mutations, and we know what to do...
with them, but we’re [also] going to find [patients] with other mutations and abnormalities, and that’s going to open a door for those [patients].”

In gastrointestinal (GI) malignancies, the KEYNOTE-177 results show that molecular testing for MSI-H/dMMR and other aberrations can identify targets with the potential to deliver clinically meaningful improvements for patients, Tanios S. Bekaii-Saab, MD, said in an interview. “We have to find every way possible to get [GI tumors] sequenced.”

In ovarian cancer, the SOLO2 data cement the role of olaparib and other PARP inhibitors in the treatment armamentarium for patients with BRCA mutations, said David M. O’Malley, MD, director of the Division of Gynecologic Oncology at The Ohio State University Comprehensive Cancer Center–James in Columbus. “Clearly, any BRCA patient who has not received a PARP inhibitor at recurrence should then receive a PARP inhibitor in the maintenance setting after platinum-based chemotherapy,” he said in an interview.

The following information provides a more detailed look at these studies.

**OSIMERTINIB AS ADJUVANT NSCLC TREATMENT**

Despite the many innovations in therapies for advanced NSCLC in the past 2 decades, investigators are still seeking to improve the cure rate for patients with early-stage disease, who typically undergo surgery followed by cisplatin-based chemotherapy, if appropriate, but then face high recurrence rates. Patients with localized/early-stage disease have a 5-year recurrence rate of 45% at stage IB, and those with regional/locally advanced cancer have recurrence rates of 62% at stage II and 76% at stage III, Roy S. Herbst MD, PhD, said in presenting the ADAURA data at ASCO 2020. He said approximately 30% of patients with newly diagnosed NSCLC present with potentially resectable disease.2

“It is clear that there remains an unmet need for novel and effective adjuvant therapies to improve clinical outcomes in the early-stage non-small cell lung cancer setting,” said Herbst, the Ensign Professor of Medicine (Medical Oncology) and chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital and associate cancer center director for translational research at Yale Cancer Center, both in New Haven, Connecticut.

Although tyrosine kinase inhibitors (TKIs) directed at EGFR-mutant NSCLC have changed the paradigm for patients with advanced and metastatic disease, their role as adjuvant therapy needs clarification. Overall, EGFR mutations have been detected in approximately 10% to 15% of patients with NSCLC in the United States and Europe and up to 40% of patients in Asia.4

Osimertinib, a third-generation EGFR inhibitor, is approved in 2 metastatic NSCLC settings: as first-line treatment for patients whose tumors harbor EGFR exon 19 deletions or exon 21 L858R mutations and for those with EGFR T790M resistance mutations and whose disease has progressed after prior EGFR-directed TKI therapy. In ADAURA, 682 patients with EGFR-mutant stage IB, II, or IIIA disease were randomized to receive osimertinib 80 mg daily versus placebo. Patients received treatment for 3 years or until disease recurrence or discontinuation criteria were met. The primary end point was investigator-assessed DFS in patients with stage II or IIIA disease. Findings reported at ASCO 2020 were from an unplanned interim analysis with a data cutoff of January 17, 2020; all patients were followed for at least 1 year, including 65% for at least 2 years and 30% for at least 3 years.

In patients with stage II or III disease, the median DFS for those who received osimertinib (n = 233) was not reached (NR; 95% CI, 38.8-40.7 months) compared with 20.4 months (95% CI, 16.6-24.5) for those who received placebo (n = 237). Osimertinib therapy delivered an 83% reduction in the risk of disease recurrence (HR, 0.17; 96% CI, 0.12-0.23; P < .0001). In the overall study population, the median DFS for participants who received osimertinib (n = 339) was NR (95% CI, 22.1-35.8) for those who took the placebo (n = 343), which translated into an HR favoring osimertinib therapy of 0.21 (95% CI, 0.16-0.28; P < .0001) (TABLE 1).3 The findings marked the first time a targeted agent demonstrated a statistically significant and clinically meaningful improvement in this population during a global randomized trial, Herbst noted. “These numbers were fantastic,” he said in an interview. “We assumed that these agents would be active, but [we didn’t realize it would be] to this extent. These data speak to the fact that these are more active third-generation agents that are more potent in areas such as the brain and the central nervous system, and they are better tolerated; patients can take them for longer [durations].”

Herbst added that the data would

### TABLE 1. DISEASE-FREE SURVIVAL FINDINGS IN ADAURA NSCLC TRIAL

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Osimertinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: patients with stage II/IIIA disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>233</td>
<td>237</td>
</tr>
<tr>
<td>Median DFS, months (95% CI)</td>
<td>NR (38.8-NR)</td>
<td>20.4 (16.6-24.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.17 (0.12-0.23); P &lt; .0001</td>
<td></td>
</tr>
<tr>
<td>Secondary end point: overall population of patients with stage IB/II/IIIA disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>339</td>
<td>343</td>
</tr>
<tr>
<td>Median DFS, months (95% CI)</td>
<td>NR (NC-NR)</td>
<td>28.1 (22.1-35.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.21 (0.16-0.28); P &lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

DFS, disease-free survival; NC, not calculable; NR, not reached; NSCLC, non–small cell lung cancer.
change practice. “I think that [the study] really heralds a new age for how we’re treating this disease,” he said. “We’re in a precision-guided world, and we have ways to target the patients with the right drug at the right time—and that time is now, an earlier time in the disease.”

Preventing metastases with molecularly targeted therapy, Herbst continued, “is a paradigm that I feel is going to be so important as we move forward in the treatment of this deadly disease.” In keeping with that message, Herbst said the results show a need for more molecular sequencing, at least for patients with nonsquamous disease, so that clinicians can identify potential therapeutic targets earlier in the treatment timeline.

Kris said expanding testing into an earlier setting for patients who undergo surgery would not be problematic because tissue would be available and an additional biopsy would not be needed. “This is a trial that will truly change how we care for [patients] with EGFR-mutant lung cancer,” he said. “I think all the patients with an EGFR mutation and a successful lung cancer surgery will be offered osimertinib after the conclusion of chemotherapy, if appropriate by their stage, and radiation, if appropriate by their stage.”

Meanwhile, the T790M resistance mutation that osimertinib initially was designed to address would no longer be a consideration if patients receive the drug in the front line, Kris said. “The T790M mutation can develop [only] if you give a drug that does not attack it. What we’re seeing now is that [patients] who get osimertinib as initial therapy just don’t get [the mutation]. We’re not going to see it going forward,” he said.

AstraZeneca, the company developing osimertinib, plans to submit the ADAURA findings for regulatory approvals.6

PEMBROLIZUMAB FOR FRONTLINE mCRC THERAPY

The importance of MSI-H/dMMR as a predictive biomarker has been growing since 2017, when the FDA granted pembrolizumab an accelerated approval for patients with unresectable or metastatic solid tumors that test positive for the marker, have progressed after prior treatment, or for which no acceptable alternatives exist. The FDA also approved the PD-1 immune checkpoint inhibitor specifically for patients with MSI-H/dMMR mCRC that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.7

Colorectal cancers that are MSI-H/dMMR, which is the result of defective DNA repair mechanisms, comprise 15% of colorectal cancers, including 5% of patients with metastatic disease, according to Thierry André, MD, a professor of medical oncology at Sorbonne Université and Hôtel Saint-Antoine in Paris, France, who presented the KEYNOTE-177 results at ASCO 2020.4

In KEYNOTE-177, investigators sought to establish a frontline benefit for pembrolizumab over standard-of-care regimens for this patient population. Eligible patients had treatment-naïve stage IV mCRC with confirmed MSI-H status by polymerase chain reaction testing or dMMR status by immunohistochemistry testing.

In all, participants were randomized 1:1 to receive either pembrolizumab (n = 153) 200 mg every 3 weeks for up to 35 cycles or investigator’s choice of chemotherapy regimens (n = 154). The control arm choices were modified FOLFOX [oxaliplatin, leucovorin, fluorouracil] or FOLFIRI [irinotecan, fluorouracil, leucovorin] with or without either bevacizumab (Avastin) or cetuximab (Erbitux). Patients in the chemotherapy arm were permitted to cross over to the immunotherapy group. The primary end points were PFS per blinded independent central review and OS.

After a median follow-up of 32 months, the median PFS with pembrolizumab was 16.5 months (95% CI, 5.4-32.4) compared with 8.2 months (95% CI, 6.1-10.2) for the standard-of-care arm. Those findings translated into an HR of 0.60 (95% CI, 0.45-0.80; P = .0002). The PFS rate for participants who received pembrolizumab versus chemotherapy was markedly higher, at 12 months (55% vs 37%, respectively) and 24 months (48% vs 19%, respectively). The overall response rate also was higher with pembrolizumab than with chemotherapy (43.8% vs 33.1%, respectively), as was the median duration of response (NR vs 10.6 months, respectively) (TABLE 2).4

“In the past, no medical treatment has shown such a difference in terms of improvement of PFS in metastatic colorectal cancer,” André said. “The study demonstrates that the majority of the 5% of patients with metastatic colorectal cancer selected by MSI status benefited greatly with the anti–PD-1 pembrolizumab compared with standard of care.”

OS findings are not yet mature; investigators will conduct a final analysis when 190 events are reached or 12 months after the second interim analysis. André said the OS results may be affected by the fact that 59% of patients in the chemotherapy arm either crossed over during the trial to receive pembrolizumab or subsequently had anti–PD-1/PD-L1 therapy.

Of note, pembrolizumab therapy was less effective in rate of progressive disease, which was 29.4% with immunotherapy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pembrolizumab (n = 153)</th>
<th>Chemotherapy-based regimen (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>16.5 (5.4-32.4)</td>
<td>8.2 (4.1-10.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.60 (0.45-0.80); P = .0002</td>
<td>0.84 (0.64-1.10); P = .2101</td>
</tr>
<tr>
<td>Overall response rate*</td>
<td>43.8%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Complete response</td>
<td>11.1%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Partial response</td>
<td>32.7%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20.9%</td>
<td>42.2%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>29.4%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

mCRC, metastatic colorectal cancer.

*Nine patients in the pembrolizumab arm and 19 in the chemotherapy-based cohort were either not evaluable for response or not assessed.
versus 12.3% with chemotherapy. “This clearly suggests that almost one-third of patients are demonstrating intrinsic resistance to PD-1-based therapy and are not benefiting from pembrolizumab,” said Michael J. Overman, MD, who served as a discussant for the abstract. He also noted that patients with an ECOG performance status score of 0 had a better PFS result with pembrolizumab than did those with a score of 1 (HR, 0.37 vs 0.84, respectively). In addition, more PFS events occurred in the pembrolizumab arm than in the chemotherapy group in the early months of the trial.

“Who these patients are is a critical question,” said Overman, a professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston. “With this progression disease rate and initial hazard ratio favoring chemotherapy over pembrolizumab in the first 6 months of therapy, what is the correct approach for symptomatic patients at risk of disease-related complications or patients with poor performance status? For example, ECOG performance status 2 or 3. At present, the NCCN [National Comprehensive Cancer Network] recommends considering immune therapy for [patients with] poor performance status in the front line.”

Meanwhile, the toxicity profile of pembrolizumab was more favorable than that of chemotherapy; the adverse events (AEs) observed with each regimen were different but consistent with prior experience, André said.

Grade 3 or greater treatment-related AEs were observed in 22% of patients who received pembrolizumab compared with 66% who had chemotherapy. The incidence of frequent all-grade AEs that were lower with pembrolizumab than with chemotherapy, respectively, included diarrhea (25% vs 52%), fatigue (21% vs 44%), and nausea (12% vs 55%). However, the occurrence of immune-mediated AEs and infusion reactions of grade 3 or greater severity were higher with pembrolizumab (9%) than with chemotherapy (2%).

“Pembrolizumab should be the new standard of care for these patients,” André said. “These data will present another step forward for biomarker-driven studies and will help bring this approach that targets MSI-high tumors into the adjuvant and neoadjuvant settings.”

The findings are highly significant for this patient population, particularly for those with colon cancer, Bekaii-Saab said. “This essentially transforms [mCRC] from a disease where we have to try chemotherapy first and fail before we go to immune therapy to [a paradigm with] patients getting immune therapy first.”

For many of the patients who respond to pembrolizumab therapy, the benefit is durable, Bekaii-Saab added. “I don’t like to use the word loosely in stage IV disease, but this is the equivalent of a cure, with remissions that are durable [and patients who] may never see chemotherapy in their lifetime,” he said.

### Table 3. Overall Survival Results from SOLO2 Ovarian Cancer Trial

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Olaparib (n = 196)</th>
<th>Placebo (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final OS findings for overall population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>51.7</td>
<td>38.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.74 (0.54-1.00)</td>
<td>P = .0537</td>
</tr>
<tr>
<td>Final OS adjusted for subsequent PARP inhibitor therapy by placebo group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>51.7</td>
<td>35.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.56 (0.35-0.97)*</td>
<td></td>
</tr>
<tr>
<td>Time to first subsequent therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>27.4</td>
<td>7.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.37 (0.28-0.48); P &lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

OS, overall survival.

*CI not reported.

**P value not reported.

Bekaii-Saab noted that 2 schools of thought exist regarding whether pembrolizumab will deliver an OS benefit over chemotherapy in this setting. “The first scenario, which a lot of people are predicting, is that the survival is not going to be much different between pembrolizumab given first versus chemotherapy. The reasoning for that is that a lot of people are saying when you give chemotherapy first, when patients progress, they are going to have access to pembrolizumab. The thought is that whether you give it first or later [will not] change overall survival,” he said.

However, Bekaii-Saab added, others believe that introducing immunotherapy sooner will be beneficial. “Because this appears to be a game changer, the sooner you change or you attack the biology of the cancer, the better you do in the long run, and therefore, you will affect survival positively.”

In his practice, Bekaii-Saab has already treated patients with MSI-H/dMMR disease with pembrolizumab in the first line, and he has considered it for biomarker-selected patients with other GI malignancies. Even if the OS findings of KEYNOTE-177 do not meet the statistical threshold for significance, the regimen has earned its frontline status, he said.

“If the survival is positive, that’s great; that just consolidates the story. If the survival is borderline better with pembrolizumab versus overall survival with chemotherapy, when you look at the big story, the big package, of prolonging life, the quality of life is much better,” Bekaii-Saab said. “I think it has changed the landscape of how we treat MSI-high colorectal cancer. This has transformed the way we treat MSI-high tumors period, beyond colorectal cancer.”

The challenge now, he added, is to determine why 60% of the patients do not respond to immunotherapy.

### Olaparib in Ovarian Cancer Maintenance

Although investigators have conducted many clinical trials in ovarian cancer over the past 2 decades, “limited progress has..."
Key ASCO Studies

“...It is remarkable that at 5 years, 28% of patients in the olaparib arm were alive and had not received subsequent therapy based on Kaplan-Meier estimates.”

—ANDRÉS PROVEDA, MD

been made in improving overall survival,” Andrés Poveda, MD, lead author of the SOLO2 study, said in presenting the findings at ASCO 2020.

Olaparib, the first PARP inhibitor to gain FDA approval, in 2014, was cleared for use in the maintenance setting for patients with BRCA-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy on December 19, 2018, based on PFS findings from the SOLO-1 trial (NCT01844986).9

For SOLO2, Poveda and colleagues reported the final OS results from a clinical trial launched in September 2013 that evaluated maintenance olaparib administered at 300 mg twice daily versus placebo in patients with BRCA-mutant, high-grade serous or endometrioid ovarian cancer who had received 2 or more lines of platinum-based chemotherapy. Participants were required to show a complete or partial response to the most recent platinum regimen. The primary end point was investigator-assessed PFS; OS was included among the time-dependent secondary end points.5

In 2017, investigators reported that patients who received olaparib achieved a median PFS of 19.1 months (95% CI, 16.3-25.7) compared with 5.5 months (95% CI, 5.2-5.8) for those who took a placebo (HR, 0.30; 95% CI, 0.22-0.41; P < .0001).10

For the final OS results, the median duration of follow-up was 5.5 years for the olaparib group and 5.4 years for those who received a placebo. In the overall trial population, median OS for patients who received maintenance olaparib (n = 196) was 51.7 months versus 38.8 months among those who took a placebo (n = 99), which translated into an HR for death of 0.74 (95% CI, 0.54-1.00; P = .0537).5

The benefit with olaparib was more extensive when findings were adjusted to reflect that 38% of patients in the placebo group subsequently received PARP inhibitor therapy. In this analysis, the median OS was 51.7 months for the olaparib group compared with 35.4 months for the placebo cohort (HR, 0.56; 95% CI, 0.35-0.97) (TABLE 3).5

“SOLO2 is the first phase 3 trial of maintenance PARP inhibitor therapy to report an overall survival rate for women with platinum-sensitive relapsed ovarian cancer and a BRCA mutation since the introduction of platinum-based chemotherapy,” said Poveda, of Initia Oncology, Hospital Quirónsalud, in Valencia, Spain.

Beyond the OS findings, Poveda noted, data on the secondary end point of time to first subsequent therapy showed a dramatic clinical benefit with olaparib therapy. “It is remarkable that at 5 years, 28% of patients in the olaparib group were alive and had not received subsequent therapy based on Kaplan-Meier estimates,” he said. “The median time to subsequent therapy was 27.4 months in the olaparib group and 7.2 months in the placebo group. The hazard ratio was 0.37, with a P value of less than .0001.”

In terms of AEs, Poveda said few additional effects stemmed from longer-term olaparib therapy. Treatment-emergent AEs for the olaparib cohort in the final analysis compared with the primary analysis, respectively, led to dose interruptions for 50% versus 45% of participants, as well as treatment discontinuations for 17% versus 11%. Overall, 22% of patients took maintenance olaparib for 5 or more years.

An AE of special interest was the development of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). In the primary analysis, 2% of patients who received olaparib and 4% of those in the placebo arm developed MDS or AML, whereas the final analysis showed 8% and 4% in the treatment arms, respectively, with those malignancies.

“The length of time since diagnosis [and] the duration of PARP inhibitor therapy are probably relevant,” said Susana N. Banerjee, MBBS, PhD, who served as a discussant on the abstract. Banerjee noted that in the SOLO1 trial, in which patients with BRCA mutations received olaparib versus placebo as first-line maintenance therapy after platinum-based chemotherapy for approximately 2 years, the incidence of MDS/AML was “much lower,” at 1% versus 0% in the placebo arm.11

“This is the first study of longtime olaparib tablet toxicities in patients who have been receiving it for some time,” said Banerjee, a consultant medical oncologist with The Royal Marsden in London, United Kingdom. “It’s important to look at the final analysis of toxicities in patients that have had long-term treatments, looking at new onset and persistent toxicities. It’s going to be very important for us to understand the risk factors of MDS and AML better and, for other phase 3 maintenance studies, to actively capture the rates of MDS and AML beyond the study treatment for our period.”

Putting the SOLO2 findings into perspective, O’Malley, The Ohio State University specialist, said the trial “is one of the most impactful studies” in the field. “As we know, it’s extremely difficult to show an overall survival benefit in patients with ovarian cancer for multiple factors, one of which is the long-term survival and the multiple agents that they will see during their course of treatment,” he said.

“We can debate whether [SOLO2] is statistically significant with the adjustment or the unadjusted [data] for crossover, but clearly there is a clinically significant improvement of nearly 13 months [for olaparib vs placebo], and an overall survival benefit essentially unheard-of in ovarian cancer is impactful in this patient population,” O’Malley said.
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Chemotherapy (CT) de-escalation using an FDG-PET/CT (F-PET) and pathological response-adapted strategy in HER2[+] early breast cancer (EBC): PHERGain Trial. Abstract 503

In patients with HER2-positive early breast cancer, the combination of trastuzumab (Herceptin) and pertuzumab (Perjeta) has shown promising pathological complete response (pCR) rates but the rates are said to still be low compared with those of the combination plus chemotherapy. In PHERGain (NCT03161353), investigators sought to identify sensitivity markers to trastuzumab/pertuzumab through early metabolic response, by 18F-fluorodeoxyglucose–positron emission tomography (PET), in an effort to de-escalate chemotherapy.

Nearly 80% of patients who started treatment without anti-HER2 therapies (n = 227) were PET responders, and of those who started dual HER2 blockade with trastuzumab and pertuzumab with or without endocrine therapy, 37.9% achieved a total pCR (95% CI, 31.6%-44.3%; P < .001). Investigators noted that results demonstrated that PET identifies patients with HER2-positive early breast cancer who are more likely to achieve pCR with trastuzumab plus pertuzumab-based therapy and that a chemotherapy-free strategy does not.
jeopardize breast-conserving surgery in this patient population.

“PET is widely available, and, while still early, if we are able to utilize this tool in the future to de-escalate therapy for patients with breast cancer, it will be an important patient-centered win by minimizing adverse effects. This is the first step.”

Validation of MAF biomarker for response prediction to adjuvant bisphosphonates in 2 clinical trials: AZURE and NSABP-B34. Abstract 513

In this analysis of 2 pivotal trials of patients with breast cancer, AZURE (NCT00072020) and NSABP B-34 (NCT0009945), investigators evaluated the levels of MAF amplification in enrolled specimens to determine whether this can serve as a predictive biomarker of response to adjuvant bisphosphonates.

The exploration data of samples in both studies showed that MAF amplification predicts response to adjuvant bisphosphonates. Only patients with MAF-negative tumors obtained a clinical benefit from adjuvant bisphosphonate. Patients with MAF amplification demonstrated a trend toward worse overall survival (OS) and disease-free survival (DFS) when treated with adjuvant bisphosphonates. The validation data suggest that MAF amplification is a clinically useful biomarker and that MAF testing should be introduced into breast cancer treatment practice.

“Bisphosphonates have a small but significant impact on breast cancer outcomes, but they also come with adverse effects. Being able to identify the population that gets the biggest benefit would help personalize care.”

Towards data-driven decision-making for breast cancer patients undergoing mastectomy and reconstruction: Prediction of individual patient-reported outcomes at two-year follow-up using machine learning. Abstract 520

Investigators designed a validated machine learning algorithm to predict individual postoperative breast satisfaction from mastectomy and breast reconstruction and ultimately help with individualized data-driven decision-making in breast cancer care. Results showed that such algorithms could be appropriate in identifying those who might benefit from alternative treatment decisions compared with those suggested by group-level evidence. For example, these algorithms may identify patients who might benefit from implant-based reconstruction rather than autologous reconstruction.

“Anecdotally, I find that many women, years after breast surgery, confide in me with ‘if I had only known’ sentiments. I think showing someone personalized prediction around breast reconstruction outcomes is a really interesting tool.”

Comprehensive profiling of androgen receptor-positive (AR+) triple-negative breast cancer (TNBC) patients (pts) treated with standard neoadjuvant therapy (NAT) +/- enzalutamide. Abstract 517

Patients with luminal androgen receptor (AR)-positive triple negative breast cancer (TNBC) are known to have lower pCR rates following neoadjuvant chemotherapy. In the nonrandomized ARTEMIS trial (NCT02276443), patients who had chemotherapy-insensitive TNBC were treated with a regimen of enzalutamide (Xtandi) and paclitaxel (n = 17). Results showed that this approach met the pCR/residual cancer burden threshold, with a 12% pCR rate (n = 2) and a 29% residual cancer burden rate (n = 5), suggesting that this type of combination may warrant further exploration in this breast cancer subtype.

“Any move toward targeting or tailoring treatment in triple-negative breast cancer is exciting.”

Tucatinib versus placebo added to trastuzumab and capcitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB). Abstract 1005

The FDA approved tucatinib (Tukysa) in combination with trastuzumab and capcitabine (Xeloda) in April 2020 for adults with advanced, unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 1 prior anti-HER2-based regimen in the metastatic setting. The approval was based on findings from the phase 2 HER2CLIMB trial (NCT02614794). Data specifically from the brain metastasis subgroup of patients demonstrated that the risk of central nervous system (CNS) progression or death was reduced by 68% (HR, 0.32; 95% CI, 0.22-0.48; P < .00001). The median CNS progression-free survival (PFS) was 9.9 months in those treated with the investigational triplet versus 4.2 months in patients treated with trastuzumab and capcitabine with placebo. The 1-year OS rates were 70.1% and 46.7%, respectively (HR, 0.58; 95% CI, 0.40-0.85; P = .005).

“This study is so novel in the unique inclusion of brain metastases. It is a big step forward for patients with HER2-positive metastatic disease.”

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Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial cancer (UC): JAVELIN Bladder 100 phase III interim analysis. Abstract LBA1

This late-breaking abstract highlighted the JAVELIN Bladder 100 (NCT02603432) findings, in which investigators observed a statistically significant improvement in OS with the combination of best supportive care plus PD-L1 inhibitor avelumab (Bavencio) versus best supportive care alone in patients with advanced urothelial carcinoma following platinum-based chemotherapy in the frontline setting. The addition of avelumab led to a median OS of 21.4 months versus 14.3 months with standard care alone (HR, 0.69; 95% CI, 0.56-0.86; P < .001). The FDA approved avelumab on June 30, 2020, as first line maintenance therapy in advanced urothelial cancer.

“The JAVELIN Bladder 100 study of maintenance avelumab addressed a very important concept: After giving 4 to 6 cycles of chemotherapy, does maintenance avelumab versus placebo in the phase 3 setting result in improved clinical outcomes? There was a very strong OS benefit favoring avelumab with an acceptable safety profile. This is a new standard with immediate change in practice.”

IMvigor010: Primary analysis from a phase III randomized study of adjuvant atezolizumab (atezo) versus observation (obs) in high-risk muscle-invasive urothelial carcinoma (MIUC). Abstract 5000

In the international, open-label, controlled, phase 3 IMvigor010 trial (NCT02450331), investigators evaluated the safety and efficacy of adjuvant atezolizumab (Tecentriq) compared with observation in 809 patients with muscle-invasive bladder cancer who were at high risk for recurrence following surgical resection. The median DFS was 19.4 months with atezolizumab versus 16.6 months with observation (HR, 0.89; 95% CI, 0.74-1.08; P = .2446). Further, the 18-month DFS rates were 51% and 49%, respectively.

The adjuvant treatment with the PD-L1 inhibitor did not significantly improve DFS versus observation in patients with muscle-invasive bladder cancer and missed the trial’s primary end point.

“Another PD-L1 inhibitor, did not meet its primary end point in a different setting in high-risk bladder cancer. Maha Hussain, MD, presented the data with adjuvant atezolizumab as part of the IMvigor010 trial. This was actually a quite anticipated trial here that did not pan out to be positive. This was a really high-risk population with half having node-positive disease after surgery.

“It was a bit of a blow to the field because we really were thinking about an adjuvant treatment for these patients to replace chemotherapy, but atezolizumab did miss this DFS end point in muscle-invasive bladder cancer versus observation. It remains difficult to reduce the risk of muscle-invasive urothelial cancer after surgery. It is important to understand that randomized clinical trials are needed to answer important, big questions like this.”

Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced renal cell carcinoma (RCC): Updated analysis of KEYNOTE-426. Abstract 5001

Earlier data from the KEYNOTE-426 trial (NCT02853331), which explored the combination of pembrolizumab (Keytruda) and axitinib (Inlyta) for the frontline treatment of patients with advanced renal cell carcinoma (RCC), led to the approval of this regimen in this setting. In an updated analysis, the combination continued to outperform the sunitinib (Sutent) comparator. At a median follow-up of 27 months, the median OS in the intention-to-treat population was not reached in the pembrolizumab/axitinib arm versus 35.7 months in the sunitinib arm. The 24-month OS rates were 74% and 66%, respectively (HR, 0.68; 95% CI, 0.55-0.85; P < .001).

“This combination of pembrolizumab and axitinib already resulted in an OS benefit. There was an update with more follow-up, and the study continued to provide an OS benefit with a hazard ratio of 0.68. The hazard ratio seems higher than previously presented with more follow-up, probably due to subsequent lines of therapies.

“The interesting thing on the study is that the rate of complete responses has increased, and these are the best responses you can wish for. There were no new signs of toxicities. It’s cemented again: Pembrolizumab plus axitinib is a very reasonable first choice in untreated RCC.”

Optimized management of nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma (RCC): a response-based phase II study (OMNIVORE). Abstract 5005

Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced renal cell carcinoma (RCC) (HCNR GU16-260). Abstract 5006

Two sequencing-based studies evaluated strategies with the PD-1 and CTLA-4 inhibitors nivolumab (Opdivo) and ipilimumab (Yervoy), respectively. In the phase 2, response-adaptive OMNIVORE trial (NCT03203473), investigators evaluated the sequential addition of 2 doses of ipilimumab to induce response in nonresponders to nivolumab, as well as the duration of nivolumab in responding patients with advanced renal cell carcinoma (RCC). Trial results showed a low partial rate conversion with this strategy (4%; n = 2), leading investigators to determine that 2 doses of
Osimertinib as adjuvant therapy in patients (pts) with stage IB–III A EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. Abstract LB5

The phase 3 ADAURA study (NCT02511106) evaluated adjuvant osimertinib (Tagrisso) in patients with stage IB, II, and IIIA EGFR-mutant non–small-cell lung cancer (NSCLC) who underwent complete tumor resection. In April 2020, it was announced that the trial would be unblinded early following a recommendation from an independent data monitoring committee, which determined overwhelming efficacy existed with the EGFR tyrosine kinase inhibitor (TKI). Osimertinib is currently approved as a frontline treatment for patients with EGFR-mutant NSCLC.

The primary end point of DFS in patients with stage II/III disease was not reached in the osimertinib arm versus 20.4 months placebo arm (HR, 0.17; 95% CI, 0.12-0.23; P < .0001). In the overall population, investigators observed a 79% reduction in the risk of disease recurrence or death with osimertinib (HR, 0.21; 95% CI, 0.16-0.28; P < .0001). The DFS rates at 2 years were 89% and 53%, respectively.

“In both studies, there were not many complete responses. This made me think that this strategy of using these agents in combination may be better. It is also important to inform the practice; I personally would not recommend sequencing unless there is really a specific reason. I would not recommend starting a patient on a PD-1 inhibitor and adding a CTLA-4 inhibitor unless there is a reason and an increased potential, theoretical risk of immune-related adverse effects.”


In Von Hippel-Lindau (VHL) disease–associated RCC, initial results of the open-label, phase 2 study of the HIF-2α inhibitor MK-6482 showed promising efficacy and tolerability in patients with VHL-associated clear cell RCC as well as responses in other VHL-related lesions, suggesting that the agent can be further explored in VHL disease.

In data presented from the phase 2 study (NCT03401788), 61 patients treated with the HIF-2α inhibitor in the front line had an overall response rate in RCC lesions of 27.9% (95% CI, 17.1%-40.8%); all were partial responses. Further, 86.9% of patients had a decrease in the size of their target lesions, and the median duration of response was not reached, with 95% of patients remaining on study therapy.

“One interesting study is actually a study in non-clear cell RCC with VHL syndrome, with Eric Jonasch, MD, and the HIF-2α inhibitor. During the 2020 Genitourinary Cancers Symposium, we presented the results in metastatic clear cell RCC, and now it’s being tested in VHL syndrome with clear-cell RCC. There is quite interesting activity with this well-tolerated HIF-2α inhibitor compound MK-6482. I look forward to seeing even more follow-up and potentially more responses happening with time. There is definitely an unmet need for treating patients with VHL, and it is so good to see a drug developed in this context.”

Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. Abstract LB5

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The primary end point of DFS in patients with stage II/III disease was not reached
Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). Abstract 9503

The immunomodulatory receptor TIGIT is a novel inhibitory immune checkpoint that is present on activated T cells and natural killer cells in NSCLC, among other malignancies. The phase 2 CITYSCAPE trial (NCT03563716) evaluated tiragolumab, a TIGIT antibody, in combination with atezolizumab as a frontline regimen in 135 patients with PD-L1–positive NSCLC.

Results showed that in the intention-to-treat population, the combination led to a clinically meaningful improvement versus placebo plus atezolizumab in ORR (37% vs 21%) and PFS (5.22 vs 3.88 months; HR, 0.58; 95% CI, 0.38-0.89). Patients with PD-L1 tumor proportion score greater than 50% saw an increased ORR with tiragolumab (66%) versus placebo (24%) and an improvement in PFS (HR, 0.30; 95% CI, 0.15-0.61).

“The addition of tiragolumab to atezolizumab improved ORR and PFS, with most of the benefit seen in the PD-L1 high group. While there is greater clinical need for patients with PD-L1 low or negative tumors, there is clearly room for improvement in the PD-L1-high subset as well. Because TIGIT is co-expressed with PD-L1, it is perhaps not surprising that the benefit was primarily in the PD-L1-high subset. If the increased responses with tiragolumab are durable and if the PFS translates to an improvement in OS, this strategy has the potential to replace the current standard of care. Larger, confirmatory trials are under way.”

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. Abstract 9504

Trastuzumab deruxtecan-nxki (Enhertu) is an antibody-drug conjugate targeting HER2. In the DESTINY-Lung01 trial, 42 patients with advanced HER2-mutant NSCLC received trastuzumab deruxtecan monotherapy and achieved a response rate of 62.9%. Median PFS was 14.0 months (95% CI, 6.4-14.0). Grade 3 and higher adverse events were noted in 64.3% and included decreased neutrophil count (26.2%) and anemia (16.7%). There were also 5 cases (11.9%) of interstitial lung disease observed.

“HER2-mutant NSCLC remains one of the few genomically defined subsets of NSCLC that does not have an approved targeted therapy. Trastuzumab deruxtecan is a candidate to fill that void. Monotherapy in DESTINY-Lung01 had a very impressive response rate and the PFS over 1 year was striking. Treatment did, however, have notable toxicity with 23.8% of patients discontinuing therapy due to an adverse event.”

Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. Abstract 9501

The immunotherapy/chemotherapy combination of nivolumab, ipilimumab, and chemotherapy versus chemotherapy alone in the frontline setting of patients with advanced NSCLC was the focus of the CheckMate 9LA trial (NCT03215706). On May 26, 2020, the FDA approved the regimen in this setting for patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.

In updated findings, the OS benefit was further improved in the nivolumaly/ipilimumab arm, at 15.6 months compared with 10.9 months in the 4 cycles of chemotherapy-alone arm (HR, 0.66; 95% CI, 0.55-0.80).

“CheckMate 9LA compared an approach of nivolumab, ipilimumab, and 2 cycles of chemotherapy to chemotherapy alone and showed a survival benefit. Although it will be difficult to resist cross-trial comparisons, particularly to the CheckMate 227 long-term data also being presented, this regimen could provide both short- and long-term benefit. The benefit does come with a higher rate of adverse events, though the limited course of chemotherapy reduces cumulative toxicity. We need to closely monitor the long-term outcomes of all of these immunotherapy-based strategies.”

CONTINUED ON PAGE 42
Evaluating a Selective FGFR Inhibitor Treatment for Advanced Cholangiocarcinoma (CCA)
An investigational, targeted, oral, chemo-free agent

The Phase 3 PROOF Trial is evaluating the efficacy and safety of infigratinib (BGJ398), a targeted, oral, chemo-free agent, vs chemotherapy in patients with unresectable locally advanced or metastatic CCA with FGFR2 fusions.

Inclusion criteria*:

• Have histologically or cytologically confirmed unresectable locally advanced or metastatic CCA†

• Have written documentation of local laboratory or central laboratory determination of FGFR2 gene fusions/translocations from tumor tissue collected before treatment

Note: Molecular testing offered by the trial, if needed.

* Additional eligibility criteria apply.
† For adults 18 years and older.

QED is focused on developing infigratinib, a potent, selective tyrosine kinase inhibitor to treat FGFR-driven diseases.

Efficacy and safety of infigratinib in CCA have not been established. Infigratinib is not currently approved by the FDA or other health authorities.

To learn more, please contact us at:

PROOF301@QEDTx.com
QEDPROOFTrial.com

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The COVID-19 and Cancer Consortium is designed for health care professionals to report patients whom they are treating for cancer and who have also tested positive for coronavirus disease 2019 (COVID-19). In April 2020, the multicenter effort gained international members—making it a worldwide collaboration—and at the time of analysis, 106 US-based institutions were included.

In total, 928 surveys were included in the analysis, with 82% of participants having solid tumors, 22% presenting with hematologic malignancies, and 12% with multiple cancers. Patients with cancer and COVID-19 had a 30-day all-cause mortality rate of 13%. In a subgroup analysis, patients who had cancer that was present and progressing (n = 102) had a 25% mortality rate.

“The COVID-19 and Cancer Consortium is a crowdsourced online platform developed for the rapid generation of information about patients with cancer who are positive for SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2].”

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma (NDMM): results of ENDURANCE (E1A11) phase III trial. Abstract LBA3

Bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (VRd) has been a frontline standard of care in patients with newly diagnosed multiple myeloma. The ENDURANCE study (NCT01863550) compared the standard with carfilzomib (Kyprolis) plus lenalidomide and dexamethasone (KRd).

The replacement of bortezomib with carfilzomib did not confer a significant benefit. The PFS from the time of induction in the KRd arm was 34.6 months versus 34.4 months in the VRd arm. The HR for KRd/VRd was 1.04 (95% CI, 0.83-1.31; P = .742). Investigators recommend that based on these data VRd remain the standard of care in multiple myeloma.

“The ECOG-ACRIN E1A11 phase 3 randomized clinical trial will show the results of 2 common triplet induction regimens in multiple myeloma. This will help systematically evaluate for efficacy and toxicity and inform clinical practice. There is also a second randomization with a maintenance question that is part of the study.”

Multiple myeloma (MM) vaccination (influenza, FV and pneumococcal, PV) rates worldwide and impact on infection, hospitalization, and death. Abstract 8528

The INSIGHT MM study (NCT02761187) was designed to better understand patient and disease characteristics in multiple myeloma both at diagnosis and at relapse through the analysis of influenza (FV) and pneumococcal (PV) vaccine patterns. The study enrolled 4318 patients from 15 countries, and they are being followed up prospectively for at least 5 years.

Investigators observed that patients who received optimal FV (n = 612), once annually before and during the study, had lower rates of hospital admissions due to infections (31%) than patients who did not receive FV (n = 1184; 36%). Further, in an univariate analysis, a lower OS was associated with those patients who did not receive FV or PV.

“Multiple myeloma is a cancer of the immune system. Infections are common reasons for hospitalization and death in myeloma. Vaccination in patients with myeloma is underutilized, based on a study of vaccination patterns in a large health system and data collected via a patient self-report online portal. “We analyzed FV and PV patterns and associated outcomes in INSIGHT MM, the largest global, prospective, observational study in myeloma to date. Global vaccination rates were low and varied by region. The US reported the highest vaccination rates and the lowest rate of deaths due to infections. Conversely, Asia had the lowest FV and PV rates and the highest incidence of deaths due to infections. Vaccination status, for both FV and PV, was an independent prognostic factor for OS on multivariate analysis. In a post-COVID-19 world, the role of infections in cancer will become increasingly important.”

HealthTree Patient Portal mediated myeloma patient-reported vaccination and antibiotic use. Abstract e20567

HealthTree is an online portal where patients with multiple myeloma can find optimal treatment options and help identify a cure; the platform also serves as a database for the research community. It is reportedly the largest single database of patients with myeloma.

Data from an investigator-submitted online survey about infection prophylaxis and vaccinations were fielded to 4944 patients. Questions included: (1) Have you ever been vaccinated in the past 5 years with a PV? (2) In the past 3 flu seasons, have you received the FV? Overall 458 patients responded, and both the FV and PV questions were fairly high in this self-selected cohort of volunteers compared with a large health system. Patient-reported interventions via an online portal may play a role in helping investigators generate research questions based on community-supplied results.

“Infection is a major cause of morbidity and mortality in multiple myeloma. Vaccines are the first line of prevention for infectious diseases. Antimicrobial prophylaxis may improve patient outcomes, but real-world use..."
The ongoing, 2-part, 2-arm DREAMM-6 (NCT03544281) trial is investigating the antibody-drug conjugate (ADC) belantamab mafodotin in combination with lenalidomide/dexamethasone (arm A) or with bortezomib/dexamethasone (arm B) in patients with relapsed/refractory myeloma previously treated with at least 1 prior line of therapy.

Investigators presented findings from arm B, in which 59 patients have been treated to date. Results were presented for 18 patients who received belantamab mafodotin 2.5 mg/kg single dose on day 1 of an every-3-week cycle. Treatment with belantamab mafodotin had an overall response rate of 78% (95% CI, 52.4%-93.6%) and a clinical benefit rate of 83% (95% CI, 58.6%-96.4%). All patients had an evaluable response, and 50% of patients had a very good partial response.

“DREAMM-6 evaluates the common bortezomib/dexamethasone backbone with the addition of this ADC. No dose-limiting toxicities were observed. The known ocular and cytopenia safety profiles were deemed acceptable, with no new safety signals identified. This, in addition to the other abstracts and ongoing trials, should give us data about a new drug we will likely have available in the clinic soon.”

“DREAMM-6 evaluates the common bortezomib/dexamethasone backbone with the addition of this ADC. No dose-limiting toxicities were observed. The known ocular and cytopenia safety profiles were deemed acceptable, with no new safety signals identified. This, in addition to the other abstracts and ongoing trials, should give us data about a new drug we will likely have available in the clinic soon.”

“The cumulative findings from both studies are welcome, because this allows our patients more options in the perioperative setting. The key message is that ‘more is not necessarily better,’ but ‘smarter is better.’ Investigators at Mayo Clinic; Mark J. Truty, MD; and ALLIANCE Investigators, Eugene J. Koay, MD, PhD, of The University of Texas MD Anderson Cancer Center, are helping establish strategies to better pick the right perioperative therapy for the right patient.”

Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC). Abstract 4508

In this phase 2 study (NCT02519348), investigators evaluated the combination of durvalumab (Imfinzi) and tremelimumab versus durvalumab or tremelimumab alone in patients with advanced hepatocellular carcinoma. The population comprised patients who had not previously received immunotherapy.
LEARN MORE ABOUT TRODELVY™ (sacituzumab govitecan-hziy) TODAY!

Join Dr. Hope S. Rugo, MD, to learn more about TRODELVY. TRODELVY is the first ADC FDA approved for adult patients with mTNBC who have received at least 2 prior therapies for metastatic disease.

INDICATION
TRODELVY™ (sacituzumab govitecan-hziy) is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

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

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

IN THIS iPUB® DR. HOPE S. RUGO WILL

- Describe the TNBC disease state
- Understand the Prescribing Information for TRODELVY, including approved indication, warnings and precautions, adverse reactions, and other safety information
- Discuss the TRODELVY mechanism of action, appropriate patient populations, and clinical data
- Explain the dosage and administration of TRODELVY, premedication requirements, and recommendations for managing treatment-related adverse reactions

JOIN THIS MULTIDISCIPLINARY EXPERT:

Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology & Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

VIEW THE iPUB® TODAY AT OncLive.com/interactive-tools/mtnbc

ADC indicates antibody-drug conjugate; TNBC, triple-negative breast cancer.

IMPORTANT SAFETY INFORMATION

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

See additional Important Safety Information continued on the next page.
IMPORTANT SAFETY INFORMATION (cont.)

Contraindications
TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

Hypersensitivity
TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY.

Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1% (6/408) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (3/408).

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting
TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with TRODELVY. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively.

Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively.

Premedicate with a two or three drug combination regimen (e.g. dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).

Withdraw TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade ≤1.

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in Patients with Reduced UGT1A1 Activity
Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

In 84% (343/408) of patients who received TRODELVY (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele and 11% (16/149) in patients homozygous for the wild-type allele.

Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.

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

Lactation
There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Adverse Reactions
Most common adverse reactions (incidence ≥25%) in patients with mTNBC are nausea (69%), neutropenia (64%), diarrhea (63%), fatigue (57%), anemia (52%), vomiting (49%), alopecia (38%), constipation (34%), rash (31%), decreased appetite (30%), abdominal pain (26%), and respiratory infection (26%).
CONTRAINDICATIONS
TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY [see Warnings and Precautions].

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

TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting. The incidence of hypersensitivity reactions occurred in 1% (6/408) of patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY.

Diabetes occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with TRODELVY. In each population, events of Grade 3-4 occurred in 9% (10/108) of mTNBC patients and 9% (36/408) of all patients treated with TRODELVY. Four out of 408 patients (<1%) discontinued treatment due to diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with TRODELVY.

Hypersensitivity
TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical trials with TRODELVY. Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 1% (6/408) of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 1% (4/408).

Pre-infusion medication for patients receiving TRODELVY is recommended. Observe patients closely for infusion-related reactions during such TRODELVY infusion and for at least 30 minutes after completion of such infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use.

Nausea and Vomiting
TRODELVY is emetogenic. Nausea occurred in 69% (74/108) of patients with mTNBC and 68% (281/408) of all patients treated with TRODELVY. 34% of patients experienced Grade 1-2 nausea; 16% (17/108) of mTNBC patients and 12% (49/408) of all patients treated with TRODELVY. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (ONCO).

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade 1 or 2. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Use in Patients with Reduced UGT1A1 Activity
Individuals who are homozygous for the uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia and may be at increased risk for other adverse reactions following initiation of TRODELVY treatment.

In 54 (343/6348) of patients who received TRODELVY (up to 10 mg/m² on days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype data available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/153) in patients heterozygous for the UGT1A1*28 allele and 11% (16/149) in patients homozygous for the wild-type allele. Closely monitor patients with reduced UGT1A1 activity for severe neutropenia. The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.

Embryo-Fetal Toxicity
Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, 53-48, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male partners with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose (see Use in Specific Populations).

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Neutropenia [see Warnings and Precautions]
- Diarrhea [see Warnings and Precautions]
- Hypersensitivity [see Warnings and Precautions]
- Nausea and vomiting [see Warnings and Precautions]

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

The data described in the Warnings and Precautions section reflect exposure to TRODELVY as a single agent in a single-arm, open-label study (IMMU-132-01) in 408 patients with mTNBC and other malignancies who had received prior systemic therapeutic regimen for advanced disease. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 and at 21-day treatment cycles at doses up to 10 mg/m² until disease progression or unacceptable toxicity.

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse reaction</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>95</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Edema</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>74</td>
<td>17</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>64</td>
<td>43</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Dehydration</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory infection*</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>54</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to dose reductions occurred in 13% of patients treated with TRODELVY, with 24% having one dose reduction and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/hepatic neutropenia. Adverse reactions occurring in ≥ 10% of patients with mTNBC in the IMMU-132-01 study are summarized in Table 2.
Neutropenia and Precautions

CONTRAINDICATIONS

Embryo-Fetal Toxicity

homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment.

Nausea and Vomiting

leading to permanent discontinuation of TRODELVY was 1% (3/408).

Hypersensitivity

TRODELVY can cause severe and life-threatening hypersensitivity. Anaphylactic reactions have been observed in clinical practice.

Table 3: Laboratory Abnormalities observed in >10% of Patients while receiving TRODELVY

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TRODELVY (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>93</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>91</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>82</td>
</tr>
<tr>
<td>Increased activated partial thromboplastin time</td>
<td>60</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>30</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>57</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>51</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>49</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>43</td>
</tr>
<tr>
<td>Decreased aspartateaminotransferase</td>
<td>39</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>35</td>
</tr>
<tr>
<td>Decreased alanineaminotransferase</td>
<td>30</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>29</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>25</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>19</td>
</tr>
</tbody>
</table>

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 a 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 other studies to other studies or to other sacituzumab govitecan products may be misleading.

The analysis of immunogenicity of TRODELVY in serum samples from 106 patients with mTNBC was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-sacituzumab govitecan-hziy antibodies. Detection of the anti-sacituzumab govitecan-hziy antibodies was done using a 3-tier approach: screen, confirm, and titer. Persistent anti-sacituzumab govitecan-hziy antibodies developed in 2% (2/106) of patients.

Drug Interactions

Effect of Other Drugs on TRODELVY

UGT1A1 Inducers

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 [see Warnings and Precautions]. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers [see Warnings and Precautions]. Avoid administering UGT1A1 inducers with TRODELVY.

Use in Specific Populations

Pregnancy

Risk Summary

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 - 4% and 15% - 20%, respectively.

Data

Animal data

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan-hziy.

Lactation

Risk Summary

There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Contraception

Females

TRODELVY can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations]. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Infertility

Females

Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential.

Pediatric Use

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

Geriatric Use

Of the patients who received TRODELVY, 19/108 (18%) patients of mTNBC and 144/408 (35%) of all patients were ≥ 65 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

Hepatic Impairment

No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin less than or equal to 1.5 x ULN and AST/ALT < 3 ULN).

The exposure of TRODELVY in patients with mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN, or bilirubin greater than 1.0 to 1.5 x ULN and AST of any level; n=12) was similar to patients with normal hepatic function (bilirubin or AST less than ULN; n=45).

The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin > 1.5 ULN, or AST and ALT > 3 ULN, or AST and ALT > 5 ULN and associated with liver metastases.

No dedicated trial was performed to investigate the tolerability of TRODELVY in patients with moderate or severe hepatic impairment. No recommendations can be made for the starting dose in these patients.

OVERDOSAGE

In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

Pharmacokinetics

SN-38 is metabolized via UGT1A1. Genetic variants of the UGT1A1 gene such as the UGT1A1*1 alelle lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from TRODELVY [see Warnings and Precautions]. Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations.

Patient Counseling Information

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

Neutropenia

Advis patients of the risk of neutropenia. Instruct patients to immediately contact their healthcare provider if they experience fever, chills, or other signs of infection [see Warnings and Precautions].

Diarrhea

Advis patients of the risk of diarrhea. Instruct patients to immediately contact their healthcare provider if they experience diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or fainness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours following the infusion [see Warnings and Precautions].

Hypersensitivity

Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, tongue, or throat swelling, urticaria, difficulty breathing, lightheadedness, dizziness, chills, rigor, wheezing, prunules, flushing, rash, hypotension or fever, that occur during or within 24 hours following the infusion [see Warnings and Precautions].

Nausea/Vomiting

Advis patients of the risk of nausea and vomiting. Premedication according to established guidelines with a two or three drug regimen for prevention of chemotherapy-induced nausea and vomiting (CMV) is also recommended. Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated. All patients should receive take-home medications for preventing and treating delayed nausea and vomiting with clear instructions. Instruct patients to immediately contact their healthcare provider if they experience uncontrolled nausea or vomiting [see Warnings and Precautions].

Embryo-Fetal Toxicity

Advise female patients to contact their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [see Use in Specific Populations].

Contraception

Advise female patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of TRODELVY [see Use in Specific Populations].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TRODELVY [see Use in Specific Populations].

Lactation

Advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY [see Use in Specific Populations].

Infertility

Advise females of reproductive potential that TRODELVY may impair fertility [see Use in Specific Populations].

Manufactured by:

Immunomedics, Inc.

300 The American Road

Morrison Plains, NJ 07950, USA.

Manufactured License No. 1737.
Investigators sought to determine whether trastuzumab increases DFS when combined with trimodality treatment (CRT) for patients with HER2-overexpressing esophageal adenocarcinoma. The phase 3 trial (NCT01196390; RTOG-1010) randomized patients 1:1 to CRT with or without trastuzumab. A total of 204 patients were eligible for evaluation. The median DFS was 19.6 months for CRT plus trastuzumab compared with 14.2 months for CRT alone (HR, 0.97; 95% CI, 0.69-1.36). The median OS was 38.5 months versus 38.9 months, respectively (HR, 1.01; 95% CI, 0.69-1.47).

"RTOG-1010 is a randomized phase 3 study that assessed the role of adding trastuzumab to CRT for HER2-expressing esophageal adenocarcinoma. Patients who were randomized to the trastuzumab/CRT arm additionally received trastuzumab for 13 cycles postoperatively. The primary end point of this study was median DFS, and the study results failed to show an improvement, although a trend was observed favoring the trastuzumab arm.

"However, this trend may be riddled with bias because this was an open-label study, and importantly, median OS was no different between both arms. These results are disappointing but important, as they emphasize the lack of benefit for trastuzumab added to CRT in patients with resectable HER2-expressing esophageal cancer."

Overall survival (OS) and long-term disease-free survival (DFS) of three versus six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration. Abstract 4004

Pooled analysis from the IDEA collaboration examined patients with stage III colon cancer who were receiving either 3 months or 6 months of adjuvant folinic acid, fluorouracil, and oxaliplatin or with capecitabine and oxaliplatin (FOLFOX/CAPOX). Previously reported data demonstrated noninferiority in 3-year DFS outcomes for overall population. With the 5-year follow-up, results showed that the OS rates were higher than historical rates, regardless of the duration of treatment. The 5-year OS rate was 82.4% for the 3-month regimen versus 82.8% for the 6-month regimen, for an absolute 5-year OS rate difference of –0.4% (95% CI, 1.5% to –2.1%). Further, the 5-year DFS rate was 69.1% versus 70.8%, respectively.

"The IDEA collaboration study results showed in the first pooled analysis of its primary end point for DFS that CAPOX, but not FOLFOX, for 3 months was as effective as 6 months in the adjuvant treatment of patients with stage III colon cancer. Importantly, there were fewer toxicities and, more specifically, significantly less lifelong debilitating neuropathy in the 3 months–treated arm. In this abstract, the IDEA authors present the eagerly awaited 5-year survival rate for 3 versus 6 months' duration of therapy.

"The authors put special and correct emphasis on the clinical context of their findings, which unmitigatedly support the use of 3 months of adjuvant CAPOX as the standard for the vast majority of stage III colon cancer cases and arguably from last year’s update for high-risk stage II or T4N0. These findings need to be widely and consistently adopted worldwide, given their clinical meaningfulness.

"Additionally, and given that fluoropyrimidines are the primary driver of benefit in the adjuvant treatment of colon cancer, I would strongly advocate against any use of oxaliplatin beyond 3 months. When making the decision to proceed with 3 additional months of therapy—such as FOLFOX use or personal preference—one should consider single-agent capecitabine for the rest of the course."

A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone for liver metastasis from colorectal cancer: JCOG0603 study. Abstract 4005

Patients with liver-only metastases from colorectal cancer reportedly have an unclear outcome from adjuvant chemotherapy following hepatectomy. In the phase 2/3 JCOG0603 trial, investigators compared the use of adjuvant mFOLFOX6 versus hepatectomy alone.

Results showed that the addition of mFOLFOX6 improved DFS, meeting the primary end point of the study, but these results did not correlate with an OS benefit.
At a median follow-up of 59.2 months, the DFS was 4.3 years with mFOLFOX6 versus 1.7 years with surgery alone (HR, 0.67; 95% CI, 0.50-0.92; \( P = .006 \)). The 1-year, 3-year, and 5-year DFS rates with mFOLFOX6 were 80.8%, 52.7%, and 49.8%, respectively. For patients who underwent hepatectomy alone, the DFS rates were 58.9%, 42.6%, and 38.7%, respectively.

The 3- and 5-year OS rates for mFOLFOX6 were 87.2% and 71.2%, respectively, versus 91.8% and 83.1% with hepatectomy alone (HR, 1.25; 95% CI, 0.78-2.00).

“The role of perioperative therapy for clearly resectable liver-only metastases [LM] from colorectal cancer [CRC] remains a subject of debate. Results from EORTC-40983 [NCT00006479] suggested a modest DFS benefit from administration of perioperative FOLFOX versus no therapy, with no meaningful change in 5-year rate of OS.

“The new EPOC study assessed the role of cetuximab [Erbitux] plus FOLFOX versus FOLFOX in the perioperative setting and found a concerning detrimental effect from the addition of cetuximab to FOLFOX. The authors of this abstract presented their findings of JCOG0603, a randomized, phase 3 study comparing the efficacy of postoperative mFOLFOX following resection of LM in CRC versus resection only. The study suggested a trend for DFS benefit but a detriment for OS. Therefore, the authors correctly concluded that postoperative FOLFOX should not be administered in patients who undergo resection for LM in CRC.

“How do we interpret this very confusing set of data coming from 3 different randomized trials over the past 10 years? It is reasonable to recommend that the best standard for patients with clearly resectable LM in CRC is surgery only. The role of perioperative or postoperative treatment with FOLFOX at best may improve DFS but not OS, with a potential detriment to OS, especially with the addition of cetuximab.

“How do we make sense of all of this? LM in CRC is a complex problem and may be dichotomous in the sense that perhaps about 30% of LM in CRC recurrences are local. In this setting, systemic therapy will not add much benefit.

“On the other hand, if LM in CRC is a first manifestation of more systemic disease, then surgery will not be curative; systemic therapy will perhaps prolong DFS but will not affect OS. In a value-based system, this will not pass the ‘muster test.’ Future research could assess in a prospective and randomized fashion the role of circulating tumor DNA as a measure of minimal residual disease and a potential predictor for the value of postoperative therapy.”
In the phase 2 INSIGHt Glioblastoma Trial (NCT02977780), researchers are using an adaptive platform trial (APT) design to move the needle in a disease that kills 95% of patients within 5 years of diagnosis.1,2

Motivated by the belief that the APT design is more conducive to testing therapeutic efficacy in GBM than the randomized control trial (RCT), INSIGHt investigators are enrolling 280 patients with newly diagnosed, unmethylated, IDH R132H-negative disease, who will be randomized 4:1 to the standard of care (SOC) control therapy or to an investigational therapy. To be eligible to participate, patients must have genotyping data that are either available or will soon become accessible, to enable investigators’ evaluation of patients’ positive or negative status for EGFR, PI3K, and CDK amplifications or mutations.2

“INSIGHt is a novel way of conducting a trial in the hope of more quickly identifying potential treatment options. The platform format is flexible and permits us to add other treatment arms that can be compared with the control arm,” said Jan Drappatz, MD, principal investigator of the trial’s site at the University of Pittsburgh Medical Center (UPMC) and associate professor of Neurology at the University of Pittsburgh School of Medicine, both in Pittsburgh, Pennsylvania.

The opportunity for adjustment that this approach affords investigators will be critical to new drug development in GBM, added Drappatz. The standard RCT can span 1 to 4 years in length; however, more than half of patients with GBM die within the first 15 months of GBM diagnosis.3 Further, in contrast with the RCT, the APT supports the simultaneous evaluation of multiple therapeutic and biomarker-based hypotheses.

“The different arms of the INSIGHt trial are testing different molecularly targeted agents that target genomic subsets of GBM,” Drappatz said.

Initial randomization and enrollment will be equal across INSIGHt’s 4 arms, with 70 patients in each. As the trial progresses, randomization probabilities will adapt based on Bayesian estimation of the biomarker-specific probability of a therapy’s ability to confer a progression-free survival (PFS) benefit. The treatment arms that are not projected to improve PFS may be closed, and new, potentially more efficacious investigational arms may be added, increasing INSIGHt’s enrollment beyond 280 patients. This adaptive algorithm will update monthly.1

At present, INSIGHt includes 3 experimental arms. Patients randomized to arm 1 will receive SOC temozolomide (Temodar) in combination with radiotherapy (RT) for a maximum of 49 days, and adjuvant abemaciclib; arm 2, the mTOR inhibitor CC-115 plus RT, followed by CC-115 monotherapy; and arm 3, temozolomide and RT, with adjuvant neratinib (Nerlynx). Individuals in the control arm will be treated with temozolomide and RT, and adjuvant temozolomide. The primary end point is overall survival (OS). Secondary end points include treatment-emergent adverse events; PFS and OS among experimental arms and biomarker subgroups; and the association between PFS and OS effects of the investigational agents (FIGURE).3

**Eligibility criteria**

- 18 years or older
- Histologically confirmed intracranial glioblastoma or gliosarcoma following maximum surgical resection with evidence that the tumor MGMT promoter is unmethylated by standard assays
- Negative immunohistochemical result for IDH1 R132H mutation
- Genotyping data that are either available or in process
- Karnofsky PS of 60 or greater
- Stable to both systemic therapy and RT
- Willing to begin RT 14 to 42 days after surgical resection
- Normal organ and marrow function
- Women of childbearing potential: a negative serum pregnancy test

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<th>Arms</th>
<th>Control: temozolomide + RT</th>
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OS, overall survival; PFS, progression-free survival; PS, performance status; RT, radiation therapy; TEAE, treatment-emergent adverse event.
Although concurrent temozolomide plus RT currently represents the SOC in GBM and has for several decades, the combination approach offers only a modest advantage. In individuals with unmethylated MGMT promoter, standard treatments offer virtually no benefit. “For patients with GBM with unmethylated MGMT promoter, current standard therapies move the needle by almost nothing. In this treatment-resistant patient subset, most of the benefit comes from radiation therapy, but temozolomide confers only very, very minimal benefits,” said Drappatz, who serves as the associate director of the Adult Neuro-Oncology Program at UPMC.

Continued efforts to advance the GBM paradigm, such as INSiGhT, are imperative to improving patient outcomes, particularly among patients with unmethylated disease, which is associated with poorer survival than methylated GBM. MGMT, a methyltransferase protein, is essential to repairing DNA damage. When the MGMT promoter is methylated, patients are more likely to respond to chemotherapy. However, MGMT is overexpressed in 60% of GBMs, resulting in resistance to alkylating chemotherapy agents such as temozolomide.

“Long-term survival is essentially not possible for patients with unmethylated GBM,” said Drappatz, who added that the 2-year survival rates are 10% and approximately 50% for unmethylated and methylated disease, respectively.

“Most patients relapse very quickly,” Drappatz said. “The average time to progression in unmethylated patients is 5 months, so these are patients who could receive a diagnosis in January and have already developed disease progression by May despite chemotherapy and radiation. These patients have a very high unmet need for [better] therapies.”

DEVELOPING BIOMARKERS

Investigators of the INSiGhT study hope to develop biomarker data that can not only support the development of targeted therapies in GBM but also optimize precision medicine in this space. In contrast to other cancers with mutually exclusive driver mutations, GBM is characterized by redundant, overlapping alterations in multiple molecular pathways, causing patients with this disease to test positive for several biomarkers.

INSiGhT will specifically study EGFR, CDK, and PIK3CA amplifications or mutations in its population to determine whether a patient’s positive status for any of these genetic abnormalities predicts patient response to any of the experimental agents under investigation. For example, abemaciclib, an anti-CDK4/6 agent that induces irreversible G1 phase cell-cycle arrest in retinoblastoma-proficient tumors, could be a suitable intervention for patients with a positive CDK result.

Similarly, neratinib, an EGFR inhibitor that regulates cell growth and differentiation, may emerge as a viable treatment option for patients with EGFR aberrations, which present in approximately 50% of patients and represent one of the molecular hallmarks of GBM, according to Drappatz. “The rationale is to block this driver mutation and determine whether these patients have a greater PFS benefit with neratinib compared with temozolomide,” he said.

CC-115 is a selective dual inhibitor of the mTOR kinases mTORC1 and mTORC2 and of DNA-dependent protein kinase; the latter is included among the PI3K-affiliated kinase subfamily of protein kinases and aids the repair of DNA double-stranded breaks.

Notably, in GBM and in other malignancies, the PI3K/AKT/mTOR signaling axis fosters cell growth, survival, and metabolism. Beyond the possible antineoplastic activity of CC-115, the agent also has the potential to confer radiation-sensitivity in GBM, although it was not developed specifically for this disease.

Although patients will initially be randomized equally across INSiGhT’s 4 treatment arms, the adaptive algorithm will incorporate any biomarker-specific survival benefit seen with the investigational therapies into its randomization procedure. For example, if monthly, updated INSiGhT data show that patients with EGFR amplification in the neratinib arm are living longer than patients with EGFR amplification in the control arm, the algorithm will increase the probability of EGFR-amplified patients’ assignment to the neratinib arm. It may also reduce the likelihood that patients with an EGFR wild-type result will be randomized to this arm.

By assessing 3 common molecular targets in INSiGhT’s population and comparing the data from the trial’s 3 experimental arms with that of its control arm, investigators will be able to determine whether the investigational therapies better extend PFS versus temozolomide and RT. “It’s debatable if there is any benefit from temozolomide in patients with unmethylated MGMT,” Drappatz said. “INSiGhT is trying to identify targeted therapies that may work better than temozolomide.”

REFERENCES

IN PATIENTS WITH RRMM WHO RECEIVED REVLIMID® (lenalidomide) AND A PI

Proceed to a POMALYST regimen

Actual patients living with multiple myeloma.

Indication
POMALYST® (pomalidomide) is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity
• POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.
• Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.

Venous and Arterial Thromboembolism
• Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient’s underlying risk factors.

POMALYST is only available through a restricted distribution program called POMALYST REMS®.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CrCl, creatinine clearance; dex, dexamethasone; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; ITT, intent-to-treat; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; ULN, upper limit of normal.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, and additional Important Safety Information on the following pages.
IN A PHASE 3 STUDY IN WHICH 94% OF PATIENTS WERE REFRACTORY TO REVLIMID*

POMALYST + dex improved median survival vs high-dose dex

OVERALL SURVIVAL (ITT POPULATION, N=455)

**30%**

POMALYST + low-dose dex reduced risk of death vs high-dose dex

Median OS: **12.4 months** (95% CI 10.4, 15.3) vs **8.0 months** (95% CI 6.9, 9.0)

(HR 0.70; 95% CI 0.54, 0.92; P=0.009)

OS Data cutoff: March 1, 2013.

POMALYST + low-dose dex doubled the median PFS of high-dose dex (primary endpoint):

3.6 months (95% CI 3.0, 4.6) vs 1.8 months (95% CI 1.6, 2.1) (HR 0.45; 95% CI 0.35, 0.59; P<0.001)\(^1\,^2\,^1\)

\(^1\)In the study, 94% of patients were refractory to REVLIMID, 79% of patients were refractory to bortezomib, and 74% were refractory to both REVLIMID and bortezomib.

\(^2\)In the Phase 3 trial, PFS and OS were based on the assessment by the Independent Review Adjudication Committee (IRAC) review at the final PFS and OS analyses.

\(^1\)PFS Data cutoff: September 7, 2012.

**Trial Design:** POMALYST was studied in a Phase 3, multicenter, randomized, open-label trial of POMALYST + low-dose dex vs high-dose dex in patients with relapsed/refractory multiple myeloma who had received at least 2 prior treatment regimens, including REVLIMID and bortezomib, and demonstrated disease progression on or within 60 days from the last therapy (ITT population, N=455). Some key exclusion criteria included serum bilirubin >2.0 mg/dL, AST/ALT >3x ULN, and CrCl <45 mL/min.\(^1\,^2\)

Patients in the POMALYST + low-dose dex arm (n=302) received 4 mg of POMALYST orally on Days 1-21 of 28-day cycles with 40 mg of low-dose dex once daily on Days 1, 8, 15, and 22 of 28-day cycles. Patients in the high-dose dex arm (n=153) received 40 mg of dex once daily on Days 1-4, 9-12, and 17-20 of 28-day cycles. Patients >75 years received 20 mg of dex in the same respective dosing schedules. Patients receiving POMALYST + low-dose dex were required to receive prophylaxis or anti-thrombotic treatment, as well as any other patient with a history of DVT or PE. The primary endpoint was PFS, and a key secondary efficacy endpoint was OS. Treatment continued until disease progression.\(^1\,^2\)

**POMALYST + dex was studied in a variety of patients including\(^1\,^3\):**

- Renal impairment\(^6\)
- Hepatic impairment\(^6\)
- Cytogenetic abnormalities\(^7\)
- Different risk classifications\(^8\)
- Varying ages\(^8\)

\(^6\)Patients in the POMALYST + dex study were excluded with CrCl <45 mL/min (according to the Cockcroft-Gault formula or 24-hour urine collection); total bilirubin >34.2 µmol/L; and liver enzyme concentrations >3x ULN.

\(^7\)In the POMALYST + dex study, 41% of patients had del13q14, del17p13, t(4;14), or t(14;16).

\(^8\)The POMALYST + dex study included a variety of risk classifications, such as ECOG performance status and ISS staging. ECOG status was 0 in 32%, 1 in 45%, 2 in 17%, and 3 in <1% of patients; ISS Stage was I-II in 64%, and III in 32% of patients.

\(^8\)Median age of patients in the POMALYST + dex study was 64 years (range: 35-87).

Support your broad range of patients with multiple myeloma who have received REVLIMID and a PI—learn about the doublet and multiple triplet regimens with POMALYST at POMALYSTHCP.com/learn
Important Safety Information (continued)

CONTRAINDICATIONS

• **Pregnancy:** POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If POMALYST is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.

• **Hypersensitivity:** POMALYST is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, anaphylaxis) to pomalidomide or any of the excipients.

WARNINGS AND PRECAUTIONS

• **Embry-Fetal Toxicity & Females of Reproductive Potential:** See Boxed WARNINGS

  - **Males:** Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 4 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm.

  - **Blood Donation:** Patients must not donate blood during treatment with POMALYST and for 4 weeks following discontinuation of POMALYST therapy because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.

• **POMALYST REMS Program:** See Boxed WARNINGS

  - Prescribers and pharmacies must be certified with the POMALYST REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive POMALYST. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

  - Further information about the POMALYST REMS program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

• **Venous and Arterial Thromboembolism:** See Boxed WARNINGS. Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient’s underlying risk factors.

• **Increased Mortality With Pembrolizumab:** In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

• **Hematologic Toxicity:** Neutropenia (46%) was the most frequently reported adverse reaction in patients taking POMALYST in clinical trials, followed by anemia and thrombocytopenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification.

• **Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor liver function tests monthly. Stop POMALYST upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

• **Severe Cutaneous Reactions:** Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These reactions can be fatal. Consider POMALYST interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue POMALYST for Grade 4 rash, exfoliative or bullous rash, or any other severe cutaneous reactions such as SJS, TEN or DRESS.

• **Dizziness and Confusional State:** In patients taking POMALYST in clinical trials, 14% experienced dizziness (1% Grade 3 or 4) and 7% a confusional state (3% Grade 3 or 4). Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

• **Neuropathy:** In patients taking POMALYST in clinical trials, 18% experienced neuropathy (2% Grade 3 in one trial) and 12% peripheral neuropathy.

• **Second Primary Malignancies:** Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.
Important Safety Information (continued)

- **Tumor Lysis Syndrome (TLS):** TLS may occur in patients treated with POMALYST. Patients at risk are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

- **Hypersensitivity:** Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to POMALYST have been reported. Permanently discontinue POMALYST for angioedema or anaphylaxis.

**ADVERSE REACTIONS**
The most common adverse reactions for POMALYST (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain, and pyrexia.

In the phase III trial, nearly all patients treated with POMALYST + low-dose dex experienced at least one adverse reaction (99%). Adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥2% higher than control) included neutropenia (51.3%), fatigue and asthenia (46.7%), upper respiratory tract infection (31%), thrombocytopenia (29.7%), pyrexia (26.7%), dyspnea (25.3%), diarrhea (22%), constipation (21.7%), back pain (19.7%), cough (20%), pneumonia (19.3%), bone pain (18%), edema peripheral (17.3%), peripheral neuropathy (17.3%), muscle spasms (15.3%), and nausea (15%). Grade 3 or 4 adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥1% higher than control) included neutropenia (48.3%), thrombocytopenia (22%), and pneumonia (15.7%).

**DRUG INTERACTIONS**
Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce POMALYST dose by 50%.

**USE IN SPECIFIC POPULATIONS**
- **Pregnancy:** See Boxed WARNINGS. If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a POMALYST pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALYST during pregnancy as well as female partners of male patients who are exposed to POMALYST. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

- **Lactation:** There is no information regarding the presence of pomalidomide in human milk, the effects of POMALYST on the breastfed child, or the effects of POMALYST on milk production. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in a breastfed child from POMALYST, advise women not to breastfeed during treatment with POMALYST.

- **Pediatric Use:** Safety and effectiveness have not been established in pediatric patients.

- **Geriatric Use:** No dosage adjustment is required for POMALYST based on age. Patients >65 years of age were more likely than patients ≤65 years of age to experience pneumonia.

- **Renal Impairment:** Reduce POMALYST dose by 25% in patients with severe renal impairment requiring dialysis. Take dose of POMALYST following hemodialysis on hemodialysis days.

- **Hepatic Impairment:** Reduce POMALYST dose by 25% in patients with mild to moderate hepatic impairment and 50% in patients with severe hepatic impairment.

- **Smoking Tobacco:** Advise patients that smoking may reduce the efficacy of POMALYST. Cigarette smoking reduces the AUC of pomalidomide by 32% by CYP1A2 induction.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, on the following pages.

**References:**
1. POMALYST [package insert], Summit, NJ: Celgene Corp.
POMALYST® (pomalidomide), capsules, for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

• POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.

• Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment (see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1 through 8.3)). POMALYST is only available through a restricted distribution program called POMALYST REMS (see Warnings and Precautions (5.2)).

Venous and Arterial Thromboembolism

• Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thrombophlebitis is recommended, and the choice of regimen should be based on assessment of the patient’s underlying risk factors (see Warnings and Precautions (5.3)).

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

POMALYST, in combination with dexamethasone, is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Multiple Myeloma

• Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALYST [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1 through 8.3)].

The recommended starting dose of POMALYST is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression. POMALYST should be given in combination with dexamethasone. POMALYST may be taken with water. Inform patients not to break, chew, or open the capsules. POMALYST may be taken with or without food.

2.2 Dose Adjustment for Toxicities

Table 1: Dose Modification Instructions for POMALYST for Hematologic Toxicities

Toxicity | Dose Modification
--- | ---
Neutropenia | • ANC <500 per mcL or febrile neutropenia (fever more than or equal to 38.5°C and ANC <1,000 per mcL)
  • ANC return to more than or equal to 500 per mcL.
  • For each subsequent drop <500 per mcL
  • Return to more than or equal to 500 per mcL.
• Interrupt POMALYST treatment, follow CBC weekly
• Resume POMALYST treatment at 3 mg daily
• Resume POMALYST treatment at 1 mg less than the previous dose.

Thrombocytopenia

• Platelets <25,000 per mcL
  • Platelets return to >50,000 per mcL
  • For each subsequent drop <25,000 per mcL
  • Return to more than or equal to 50,000 per mcL.
• Interrupt POMALYST treatment, follow CBC weekly
• Resume POMALYST treatment at 3 mg daily
• Resume POMALYST treatment at 1 mg less than previous dose.

ANC, absolute neutrophil count

To initiate a new cycle of POMALYST, the neutrophil count must be at least 500 per mcL and the platelet count must be at least 50,000 per mcL. If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST.

Permanently discontinue POMALYST for angioedema, anaphylaxis, Grade 4 rash, skin exfoliation, bullae, or any other severe dermatologic reaction [see Warnings and Precautions (5.7)].

For other Grade 3 or 4 toxicities, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician’s discretion.

2.3 Dose Adjustment for Strong CYP1A2 Inhibitors

Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce POMALYST dose by 50% [see Drug Interactions (7.1)].

2.4 Dose Adjustment for Patients with Severe Renal Impairment on Hemodialysis

For patients with severe renal impairment requiring dialysis, the recommended starting dose is 3 mg daily (25% dose reduction). Take POMALYST after completion of dialysis procedure on hemodialysis days (see Use in Specific Populations (8.6)).

2.5 Dose Adjustment for Patients with Hepatic Impairment

For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction) [see Use in Specific Populations (8.7)].

4 CONTRAINdications

4.1 Pregnancy

POMALYST is contraindicated in females who are pregnant. POMALYST can cause fetal harm when administered to a pregnant female [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.

4.2 Hypersensitivity

POMALYST is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactoid) to pomalidomide or any of the excipients [see Warnings and Precautions (5.7), Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

POMALYST is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death [see Use in Specific Populations (8.1)]. POMALYST is only available through the POMALYST REMS program [see Warnings and Precautions (5.2)].

Females of Reproductive Potential

• Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning POMALYST therapy, during therapy, during dose interruptions, and for at least 4 weeks after completing therapy.

• Females must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing POMALYST therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles [see Use in Specific Populations (8.3)].

Males

Pomalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 4 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm [see Use in Specific Populations (8.3)].

Blood Donation

Patients must not donate blood during treatment with POMALYST and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.

5.2 POMALYST REMS® Program

Because of the embryo-fetal risk [see Warnings and Precautions (5.1)], POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the “POMALYST REMS” program.

Required components of the POMALYST REMS program include the following:

• Prescribers must be certified with the POMALYST REMS program by enrolling and complying with the REMS requirements.

• Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.3)] and males must comply with contraception requirements [see Use in Specific Populations (8.3)].

• Pharmacies must be certified with the POMALYST REMS program, must only dispense to patients who are authorized to receive POMALYST and comply with REMS requirements.

Further information about the POMALYST REMS program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

5.3 Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial
Thromboembolic events (myocardial infarction and stroke) have been observed in patients treated with POMALYST and low-dose dexamethasone (Low-dose Dex). In Trial 2, where pembrolizumab was added to a thalidomide analogue and dexamethasone, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is recommended outside of controlled clinical trials.

5.4 Increased Mortality in Patients With Multiple Myeloma When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone

In two randomized clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is recommended outside of controlled clinical trials.

5.5 Hematologic Toxicity

In trials 1 and 2 in patients who received POMALYST + Low-dose Dex, neutropenia was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 51% of patients in both trials. The rate of Grade 3/4 neutropenia was 46%. The rate of febrile neutropenia was 8%.

Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification of treatment based on the patient’s underlying risk factors.

5.6 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor hepatic function tests monthly. Stop POMALYST upon elevation of liver enzymes and evaluate. After return to baseline values, treatment at a lower dose may be considered.

5.7 Severe Cutaneous Reactions

Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocardiitis, and/or pericarditis. These reactions can be fatal. Consider POMALYST interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue POMALYST for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or DRESS (see Dosage and Administration [2.2]).

5.8 Dizziness and Confusional State

In trials 1 and 2 in patients who received POMALYST + Low-dose Dex, 14% of patients experienced dizziness and 7% of patients experienced a confusional state; 1% of patients experienced Grade 3 dizziness, and 2% of patients experienced Grade 3 or 4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

5.9 Neutropathy

In trials 1 and 2 in patients who received POMALYST + Low-dose Dex, 18% of patients experienced neutropenia, with approximately 12% of the patients experiencing peripheral neutropenia. Two percent of patients experienced Grade 3 neutropenia in trial 1. There were no cases of Grade 4 neutropathy adverse reactions reported in either trial.

5.10 Risk of Second Primary Malignancies

Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

5.11 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in patients treated with pembrolizumab. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.12 Hypersensitivity

Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to POMALYST have been reported. Permanently discontinue POMALYST for angioedema or anaphylaxis (see Dosage and Administration [2.2]).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in detail in the Prescribing Information labeling sections:

- **Fetal Risk** [see Boxed Warning, Warnings and Precautions (5.1, 5.2)]
- Venous and Arterial Thromboembolism [see Boxed Warning, Warnings and Precautions (5.3)]
- Increased Mortality in Patients with Multiple Myeloma When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone [see Warnings and Precautions (5.4)]
- **Hematologic Toxicity** [see Warnings and Precautions (5.5)]
- **Hepatotoxicity** [see Warnings and Precautions (5.6)]
- **Severe Cutaneous Reactions** [see Warnings and Precautions (5.7)]
- **Dizziness and Confusional State** [see Warnings and Precautions (5.8)]
- Neutropenia [see Warnings and Precautions (5.9)]
- **Risk of Second Primary Malignancies** [see Warnings and Precautions (5.10)]
- **Tumor Lysis Syndrome** [see Warnings and Precautions (5.11)]
- **Hypersensitivity** [see Warnings and Precautions (5.12)]

6.1 Clinical Trials Experience

Multiple Myeloma

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.

In Trial 1, data were evaluated from 219 patients (safety population) who received treatment with POMALYST alone (N=107) or POMALYST + Low-dose Dex (N=112). In Trial 2, data were evaluated from 450 patients (safety population) who received treatment with POMALYST + Low-dose Dex (300 patients) or High-dose Dexamethasone (High-dose Dex) (150 patients). The median number of treatment cycles for the POMALYST + Low-dose Dex arm was 5. In the POMALYST + Low-dose Dex arm, 67% of patients had a dose interruption of POMALYST, the median time to the first dose interruption of POMALYST was 4.1 weeks. Eighteen percent of patients had a dose reduction of POMALYST, the median time to the first dose reduction of POMALYST was 4.5 weeks. Eight percent of patients discontinued POMALYST due to adverse reactions.

Tables 2 and 3 summarize the adverse reactions reported in Trials 1 and 2, respectively.

Adverse reactions ≥10% in either arm, respectively:

- **Blood and lymphoid system disorders:** Neutropenia (48%, 41%), Anemia (25%, 21%), Thrombocytopenia (16%, 10%), Leukopenia (7%, 10%), Febrile neutropenia (6%, 3%), Lymphopenia (2%, 7%)
- **Gastrointestinal disorders:** Nausea (36%, 24%), Constipation (36%, 37%), Diarrhea (35%, 36%), Vomiting (14%, 14%), Musculoskeletal and connective tissue disorders: Back pain (35%, 32%), Musculoskeletal chest pain (23%, 20%), Muscle spasms (22%, 20%), Arthralgia (17%, 15%), Muscular weakness (14%, 13%), Bone pain (12%, 7%), Musculoskeletal pain (12%, 17%), Pain in extremity (6%, 14%), Infections and infestations: Upper respiratory tract infection (37%, 29%), Pneumonia (28%, 34%), Urinary tract infection (10%, 17%), Sepsis (<10%, <10%)
- **Metabolism and nutrition disorders:** Decreased appetite (23%, 19%), Hypercalcemia (22%, 12%), Hypokalemia (11%, 15%), Hyperglycemia (11%, 14%), Hypercholesterolemia (<10%, <10%), Hypoglycemia (6%, 12%)
- **Respiratory, thoracic and mediastinal disorders:** Cough (36%, 46%), Cough with expectoration (17%, 11%), Productive cough (9%, 13%), Orpharyngeal pain (0%, 0%), Skin and subcutaneous tissue disorders: Rash (23%, 19%), Perineal rash (11%, 13%), Dermatitis (58%, 63%), Edema peripheral (20%, 18%), Nervous system disorders: Dizziness (22%, 18%), Peripheral neuropathy (22%, 18%), Headache (15%, 10%), Tremor (10%, 13%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%), Skin and subcutaneous tissue disorders: Rash (21%, 16%), Pruritus (15%, 9%), Dry skin (0%, 0%), Night sweats (0%, 0%)
Investigations: Blood creatinine increased\(^6\) (6%, 3%), Weight decreased (0%, 0%), Weight increased (0%, 0%), Psychiatric disorders: Anxiety (0%, 0%), Confusional state\(^6\) (6%, 3%), Insomnia (0%, 0%); Renal and urinary disorders: Renal failure (8%, 7%).

* Regardless of attribution of relatedness to POMALYST.

\( ^{a} \) POMALYST alone arm includes all patients randomized to the POMALYST alone arm who took study drug; 61 of the 107 patients had dexamethasone added during the treatment period.

b Serious adverse reactions were reported in at least 2 patients in any POMALYST treatment arm. Data cutoff: 01 March 2013

In Trial 2 of 450 patients who received POMALYST + Low-dose Dex (N=300) or High-dose Dex (N=150), at least one adverse reaction was reported in 99% of patients.

All Adverse Reactions \(\geq 5\%\) in POMALYST + Low-dose Dex arm and at least 2% higher than the High-dose-Dex arm included:

**Blood and Lymphatic System Disorders:**
- Neutropenia (51%, 21%)
- Thrombocytopenia (30%, 29%)\(^a\)
- Leukopenia (13%, 5%)
- Febrile neutropenia\(^a\) (9%, 0%)
- General disorders and administration site conditions:
  - Fatigue and weakness (24%, 43%)
  - Edema peripheral (17%, 11%)
  - Pain (4%, 2%)\(^a\)
  - Infections and infestations:
    - Upper respiratory tract infection\(^6\) (31%, 13%)
    - Pneumonia\(^b\) (19%, 12%)
    - Neutropenic sepsis\(^b\) (1%, 0%)
  - Gastrointestinal disorders:
    - Diarrhea (22%, 15%)
    - Constipation (22%, 15%)
    - Nausea (15%, 10%)
    - Vomiting (8%, 4%)
  - Headache (8%, 5%)
  - Tremor (6%, 1%)
  - Depressed level of consciousness (2%, 0%)\(^a\)
  - Hyperkalemia (25%, 17%)
  - Cough (20%, 10%)
  - Chronic obstructive pulmonary disease\(^b\) (2%, 0%)
  - Nervous system disorders:
    - Peripheral neuropathy (17%, 12%)
    - Dizziness (12%, 9%)
    - Headache (8%, 5%)
    - Tremor (8%, 1%)
  - Depressed level of consciousness (2%, 0%)\(^a\)
  - Metabolism and nutrition disorders:
    - Decreased appetite (15%, 8%)
    - Hypokalemia (9%, 8%)
    - Hypocalcemia (4%, 6%)
  - Skin and subcutaneous tissue disorders:
    - Rash (8%, 1%)
    - Pruritus (7%, 3%)
    - Hyperhidrosis (5%, 1%)
    - Interstitial lung disease (2%, 2%)
    - Pelvic pain (2%, 2%)

In Trial 2, Grade 3/4 at least one adverse reaction was reported in 86% of patients treated with POMALYST + Low-dose Dex (N=300) and 85% with POMALYST + Low-dose Dex arm, and at least 1% point higher than the High-dose-Dex arm included:

**Blood and Lymphatic System Disorders:**
- Neutropenia\(^a\) (48%, 16%)
- Thrombocytopenia (22%, 26%)
- Leukopenia (0%, 9%)
- Febrile neutropenia\(^a\) (9%, 0%)
- General disorders and administration site conditions:
  - Fatigue and aches\(^a\) (9%, 12%)
  - Pyrexia\(^a\) (8%, 5%)
  - Edema peripheral (1%, 2%)
  - Pain (2%, 1%)
  - Infections and infestations:
    - Upper respiratory tract infection\(^b\) (3%, 1%)
    - Pneumonia\(^b\) (16%, 10%)
    - Neutropenic sepsis\(^b\) (1%, 0%)
  - Gastrointestinal disorders:
    - Diarrhea (1%, 1%)
    - Constipation (2%, 0%)
    - Nausea (1%, 1%)
    - Vomitting (1%, 0%)
    - Musculoskeletal and connective tissue disorders:
      - Back pain\(^a\) (5%, 4%)
      - Bone pain\(^a\) (7%, 5%)
      - Muscle spasms (0%, 1%)
    - Arthralgia (1%, 1%)
    - Pain in extremity (2%, 0%)
  - Renal and urinary disorders:
    - Renal failure (7%, 5%)
    - Lower urinary tract infection\(^b\) (1%, 0%)
    - Bladder disorders:
      - Prolapse\(^b\) (1%, 0%)
  - Reproductive system and breast disorders:
    - Vomiting (11%, 1%)
    - Breast disorders:
      - Pelvic pain (1%, 0%)
    - Skin and subcutaneous tissue disorders:
      - Rash (1%, 1%)
      - Pruritus (3%, 5%)
      - Hyperhidrosis (5%, 1%)
  - Metabolism and nutrition disorders:
    - Decreased appetite (1%, 1%)
    - Hypokalemia (4%, 3%)
    - Hypocalcemia (2%, 1%)

Skin and Subcutaneous Tissue Disorders:
- Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)

7 DRUG INTERACTIONS

7.1 Drugs That Affect Pomalidomide Plasma Concentrations

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A4. Pomalidomide is also a substrate for P-glycoprotein (P-gp).

CYP1A2 inhibitors:
- In healthy volunteers, co-administration of fluvoxamine, a strong CYP1A2 inhibitor, increased C\(_{\text{max}}\) and AUC of pomalidomide by 24% and 125% respectively. Increased pomalidomide exposure increases the risk of exposure related toxicities.

Avoid co-administration of strong CYP1A2 inhibitors (e.g. ciprofloxacin and fluvoxamine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALYST during pregnancy as well as female partners of male patients who are exposed to POMALYST. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Risk Summary

- Based on the mechanism of action and findings from animal studies, POMALYST can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy (see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)).
- POMALYST is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as anemia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of cartilage, and facial abnormalities (anophthalmos, microphthalmos, and congenital heart defects).
- Although thalidomide and its metabolites do not cross the placenta, a significant degree of malformations have also been documented, and mortality at or shortly after birth has been reported in about 40% of infants.
- Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide crossed the placenta after administration to pregnant rabbits (see Data).
- If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.
- If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.
- The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

- Adverse Data
- Pomalidomide was teratogenic in both rats and rabbits in the embryo-fetal developmental studies when administered during the period of organogenesis.
- In rats, pomalidomide was administered orally to pregnant animals at doses of 20 to 100 mg/kg/day. Malformations or absence of urinary bladder, absence of
thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central, and transverse arches) were observed at all dose levels. There was no maternal toxicity observed in this study. The lowest dose in rats resulted in an exposure (AUC) approximately 85-fold of the human exposure at the recommended dose of 4 mg/day. Other embryo-fetal toxicities included increased resorptions leading to decreased number of viable fetuses.

In rabbits, pomalidomide was administered orally to pregnant females at doses of 10 to 250 mg/kg/day. Additional cardiac malformations such as interventricular septal defect were seen at all doses with increased incidences at 250 mg/kg/day. Additional malformations observed at 250 mg/kg/day included anomalies in limbs (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digits) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs, and a reduced average for ossified tarsals.

No maternal toxicity was observed at the low dose (10 mg/kg/day) that resulted in cardiac anomalies in fetuses; this dose resulted in an exposure (AUC) approximately equal to that reported in humans at the recommended dose of 4 mg/day. Additional embryo-fetal toxicity included increased resorption.

Following daily oral administration of pomalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma pomalidomide concentrations were approximately 50% of the maternal Cmax at all dosages (5 to 250 mg/kg/day), indicating that pomalidomide crossed the placenta.

8.2 Lactation
Risk Summary
There is no information regarding the presence of pomalidomide in human milk, the effects of POMALYST on the breastfed child, or the effects of POMALYST on the breastfed child, or the effects of POMALYST on milk production. Pomalidomide was not detected in human milk. No adverse effects of pomalidomide have been reported in nursing infants when exposed to maternal plasma concentrations in the range of 0.63 to 1.46.

8.3 Females and Males of Reproductive Potential

POMALYST can cause fetal harm when administered during pregnancy [see Use in Specific Populations (8.1)]. Verify the pregnancy status of females of reproductive potential prior to initiating POMALYST therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking POMALYST, during dose interruptions and for at least 4 weeks after completing therapy. Females of reproductive potential must have 2 negative pregnancy tests before initiating POMALYST. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALYST. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. POMALYST treatment must be discontinued during this evaluation.

Contraception
Females
Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner’s vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Males
Pomalidomide is present in the semen of males who take POMALYST. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 4 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm.

Infertility
Based on findings in animals, female fertility may be compromised by treatment with POMALYST [see Nonclinical Toxicology (13.1)].

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

8.5 Geriatric Use
No dosage adjustment is required for POMALYST based on age. Of the total number of patients in clinical studies of POMALYST, 44% were aged older than 65 years, while 16% were aged older than 75 years. No overall differences in effectiveness were observed between these patients and younger patients. In these studies, patients older than 65 years were more likely than patients less than or equal to 65 years of age to experience pneumonia.

8.6 Renal Impairment
In patients with severe renal impairment requiring dialysis, the AUC of pomalidomide increased by 38% and the rate of SAE increased by 64% relative to patients with normal renal function; therefore, starting dose adjustment is recommended. For patients with severe renal impairment requiring dialysis, POMALYST should be administered at the completion of hemodialysis on dialysis days because exposure of pomalidomide could be significantly decreased during dialysis [see Dosage and Administration (2.4)].

8.7 Hepatic Impairment
Pomalidomide is metabolized primarily by the liver. Following single dose administration, the AUC of pomalidomide increased 51%, 56%, and 72% in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. Dose adjustment is recommended in patients with hepatic impairment [see Dosage and Administration (2.5)].

8.8 Smoking Tobacco
Cigarette smoking reduces pomalidomide AUC by 32% due to CYP1A2 induction. Advise patients that smoking may reduce the efficacy of pomalidomide.

10 OVERDOSAGE
Hemorrhagia can remove pomalidomide from circulation.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of 12 monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 16-fold of the exposure
POMALYST REMS Program
Because of the risk of embryo-fetal toxicity, POMALYST is only available through a restricted program called POMALYST REMS [see Warnings and Precautions (5.2)].

- Patients must sign a Patient-Physician Agreement Form and comply with the requirements to receive POMALYST. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements, and participate in monthly telephone surveys. Males must comply with the contraception requirements [see Use in Specific Populations (8.3)].
- POMALYST is available only from pharmacies that are certified in POMALYST REMS program. Provide patients with the telephone number and website for information on how to obtain the product.

Pregnancy Exposure Registry
Inform females that there is a Pregnancy Exposure Registry that monitors pregnancy outcomes in females exposed to POMALYST during pregnancy and that they can contact the Pregnancy Exposure Registry by calling 1-888-423-5436 [see Use in Specific Populations (8.1)].

Venous and Arterial Thromboembolism
Inform patients of the risk of developing DVT, PE, MI, and stroke and to report immediately any signs and symptoms suggestive of these events for evaluation [see Boxed Warning and Warnings and Precautions (5.3)].

Hematologic Toxicities
Inform patients on the risks of developing neutropenia, thrombocytopenia, and anemia and the need to report signs and symptoms associated with these events to their healthcare provider for further evaluation [see Warnings and Precautions (5.7)].

Hepatotoxicity
Inform patients on the risks of developing hepatotoxicity, including hepatic failure and death, and to report signs and symptoms associated with these events to their healthcare provider for evaluation [see Warnings and Precautions (5.6)].

Severe Cutaneous Reactions
Inform patients of the potential risk for severe skin reactions such as SJS, TEN and DRESS and to report any signs and symptoms associated with these reactions to their healthcare provider for evaluation [see Warnings and Precautions (5.7)].

Dizziness and Confusional State
Inform patients of the potential risk of dizziness and confusion with the drug, to avoid situations where dizziness or confusional state may be a problem, and not to take other medications that may cause dizziness or confusional state without adequate medical advice [see Warnings and Precautions (5.8)].

Neuropathy
Inform patients of the risk of neuropathy and to report the signs and symptoms associated with these events to their healthcare provider for further evaluation [see Warnings and Precautions (5.9)].

Second Primary Malignancies
Inform patients that the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown [see Warnings and Precautions (5.10)].

Tumor Lysis Syndrome
Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.11)].

Hypersensitivity
Inform patients of the potential for severe hypersensitivity reactions such as angioedema and anaphylaxis to POMALYST. Instruct patients to contact their healthcare provider right away for any signs and symptoms of these reactions. Advise patients to seek emergency medical attention for signs or symptoms of severe hypersensitivity reactions [see Warnings and Precautions (5.12)].

Smoking Tobacco
Advise patients that smoking tobacco may reduce the efficacy of POMALYST [see Use in Specific Populations (8.8)].

Dosing Instructions
Inform patients on how to take POMALYST [see Dosage and Administration (2.1)]

- POMALYST should be taken once daily at about the same time each day.
- Patients on hemodialysis should take POMALYST following hemodialysis, on hemodialysis days.
- POMALYST may be taken with or without food.
- The capsules should not be opened, broken, or chewed. POMALYST should be swallowed whole with water.
- Instruct patients that if they miss a dose of POMALYST, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take POMALYST at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
Summit, NJ 07901
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UGN-102 Emerges As Potential Surgical Alternative for Low-Grade, Intermediate-Risk NMIBC

by LISA ASTOR

Primary Chemoablation with UGN-102 (mitomycin) elicited encouraging responses in patients with low-grade, intermediate-risk non-muscle-invasive bladder cancer (NMIBC) and may consequently be an appropriate nonsurgical treatment intervention for patients, according to interim results from the phase 2b OPTIMA II trial (NCT03558503) presented at the 2020 American Urological Association (AUA) Annual Meeting.1,2

Notably, 65% of patients achieved complete responses (CRs) just 3 months after initiating treatment with UGN-102.1 UGN-102 is a reverse thermogelatin hydrogel that contains mitomycin. A standard urinary catheter delivers the gel formation into the body at a low temperature. Once it liquifies, the formulation warms to body temperature and becomes a gel for exposure to mitomycin for up to 6 hours in the bladder, investigator William C. Huang, MD, explained.

“These interim data demonstrate that primary chemoablation of low-grade, intermediate-risk non-muscle-invasive bladder cancer using UGN-102 results in a significant treatment response and encouraging durability,” said Huang, associate professor, Department of Urology at NYU Grossman School of Medicine, and chief, Urology Service, at NYU Langone’s Tisch Hospital in New York, New York. “The interim results from OPTIMA II indicate that UGN-102, if approved, may provide an effective, nonsurgical treatment option for these patients that is both well tolerated and durable.”2

Transurethral resection of the bladder (TURBT) and intravesical therapy are the standard of care for treating patients with low-grade, intermediate-risk NMIBC, which is defined by the presence of multiple and/or recurrent low-grade Ta tumors. The use of a single intravesical instillation of mitomycin C after TURBT was previously shown to reduce the risk of recurrence in patients with NMIBC.3

OPTIMA II was initiated to explore the efficacy and safety of UGN-102 for primary chemoablation in patients with low-grade, intermediate-risk NMIBC as a nonsurgical alternative to TURBT. The trial is an ongoing prospective, single-arm, open-label phase 2 study.

Intermediate risk was defined as disease with multiple tumors, a solitary tumor greater than 3 cm, and/or at least 1 occurrence within a year of diagnosis. Patients with negative voiding cytology for high-grade disease were also eligible to enroll. The trial excluded patients with a history of carcinoma in situ in the prior 5 years, high-grade papillary urothelial carcinoma (UC) within the prior 2 years, or bacillus Calmette-Guerin treatment for UC within the prior 2 years. Patients with prior or current muscle-invasive or metastatic UC or concurrent upper tract UC were also excluded.

A total of 63 patients were enrolled and treated with 6 once-weekly instillations of UGN-102. Patients were evaluated after 3 months for the primary end point of CR rate and followed for durability at the 6-, 9-, and 12-month visits. Safety was a secondary end point. The mean age of all patients was 70.5 years (range, 33-96), and men made up 60% of the population.

Ninety-eight percent of patients had noninvasive papillary carcinoma, and 82% had multiple tumors.

As of the interim analysis, 36 patients were evaluable for response duration at 6 months, with 35 maintaining their response (97.2%; 95% CI, 85.5%-99.9%). At 9 months, 24 of 28 evaluable patients had an ongoing CR (85.7%; 95% CI, 67.3%-96.0%), and 11 of 13 evaluable patients (84.6%; 95% CI, 54.6%-98.1%) had durable CRs at 1 year.

Ninety-one percent of patients had at least 1 adverse event (AE), 64% had a study drug- or procedure-related treatment-emergent AE, and 6 patients (10%) discontinued treatment because of a treatment-emergent AE. One patient (1.6%) died as a result of an AE, and 5 patients (7.9%) had at least 1 serious AE.

The most common AEs observed with UGN-102 treatment were on the lower urinary tract, Huang said, and consisted of dysuria (41%), pollakiuria (19%), hematuria (14%), fatigue (13%), micturition urgency (13%), and urinary tract infection (11%).

uroGen Pharma, the developer of UNG-102, gained FDA approval in April 2020 for the use of mitomycin gel (UGC-101; Jelmyto) in low-grade upper tract urothelial cancer.

References
FINDINGS FROM A PREPLANNED analysis of the phase 4 CARD study (NCT02485691) demonstrated superior patient-reported outcomes (PROs) with cabazitaxel (Jevtana) in men with castration-resistant prostate cancer (mCRPC) who received prior docetaxel and androgen receptor (AR)-targeted therapy versus alternative AR-targeted treatment options.

Data presented at the 2020 American Urological Association (AUA) Annual Meeting showed that cabazitaxel improved pain response compared with abiraterone acetate (Zytiga) or enzalutamide (Xtandi) in 45.9% and 19.3% of patients, respectively (P < .0001). Patients on cabazitaxel had longer time to pain progression (HR, 0.55; 95% CI, 0.32-0.97; P = .03) compared with those treated with AR-targeted agents.

The time to symptomatic skeletal events was also significantly delayed with cabazitaxel compared with AR-targeted therapy (HR, 0.59; 95% CI, 0.35-1.01; P = .05; TABLE1,2). These events have a large impact on quality of life for patients with mCRPC, according to Gero Kramer, MD, who presented the findings during the virtual meeting.

Cabazitaxel had a manageable safety profile, as well as fewer cardiac disorders compared with the control arm (4.8% vs 0.8%, respectively). Only 3.2% of patients given cabazitaxel had febrile neutropenia due to prophylactic granulocyte colony-stimulating factor given for each cycle.

Data regarding PROs were measured using the 5-level EuroQol Group’s 5-Dimension (EQ-5D-5L) questionnaire. Patient scores were evaluated at baseline, on the first day of each cycle (every 3 weeks), and at the final treatment visit. Patients were required to receive at least 1 dose of cabazitaxel or AR-targeted therapy, have an EQ-5D-5L assessment at baseline, and complete a minimum of 1 subsequent evaluation to be eligible to participate. Investigators also performed a mixed-effect model repeated measures analysis of EQ-5D-5L changes from baseline.

The 5 health domains assessed by the generic house status utility instrument EQ-5D-5L are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These domains are rated on a Likert-type scale, with 5 options: no problems, slight problems, moderate problems, severe problems, and extreme problems. Visual analog scale (VAS) is rated from 0 to 100 for overall health.

Changes in utility index scores and VAS from baseline both during treatment and at the end of treatment (EOT) favored cabazitaxel. The least squares mean difference ranged from 0.04 to 0.08 (0.05 at EOT) for utility index and 1.6 to 6.4 (5.9 at EOT) for VAS between cabazitaxel and AR-targeted therapy. Both groups had a 0.70 mean utility score at baseline and a comparable VAS (65.8, cabazitaxel; 66.3, AR-targeted therapy).

Among the patients treated with cabazitaxel, 45 (39.1%) reported moderate to severe or extreme pain/discomfort evaluated by EQ-5D-5L at baseline; 47 (40.9%) reported same with AR-targeted therapy. “Changes in VAS and utility score of EQ-5D-5L numerically favored cabazitaxel,” Kramer, an associate professor of urology in the Department of Urology at the Medical University of Vienna, in Austria, said of the data. “Results support the use of cabazitaxel over abiraterone or enzalutamide as a standard of care in patients previously treated with docetaxel who progressed within 12 months with alternative AR-targeted therapy.”

The CARD trial enrolled 255 patients, 230 of whom were evaluable for EQ-5D-5L.1 In previously reported results of CARD, cabazitaxel significantly improved median radiographic progression-free survival (PFS) by more than 4 months (8.0 months vs 3.7 months; HR, 0.54; 95% CI, 0.40-0.73; P < .001). Median overall survival with cabazitaxel was 13.6 months versus 11.0 months for patients receiving abiraterone or enzalutamide (HR, 0.64; 95% CI, 0.46-0.89; P = .0078).2

CARD was a multicenter, randomized, open-label study of patients with mCRPC who had progressed within 12 months of receiving AR-targeted therapy before or after docetaxel. Patients were randomized 1:1 to cabazitaxel every 3 weeks plus prophylactic granulocyte colony-stimulating factor or abiraterone or enzalutamide once daily. The median follow-up was 9.2 months, and the primary end point was radiographic PFS. Secondary end points included overall survival, PFS, prostate-specific antigen response, and tumor response. ■

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

**TABLE.** Key Outcomes Measures and PROs From the CARD Study1,2

<table>
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BPI-SF, brief pain inventory short form; NA, not available; NR, not reached; OS, overall survival; PRO, patient-reported outcome; rPFS, radiographic progression-free survival; SSE, symptomatic skeletal events.

*Defined as a decrease of 30% or more from baseline in average BPI-SF pain intensity score at 2 consecutive evaluations that were 3 weeks or more apart without an increase in analgesic usage score.

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New Sequencing Strategies Are Needed in Endometrial Cancer

by JESSICA HERGERT

THE EXPANSION OF TARGETED and systemic therapies for patients with recurrent, metastatic, or high-risk endometrial cancer creates a need for studies that shed light on optimal sequencing strategies, according to Brian M. Slomovitz, MD.

Regimens used to treat endometrial cancer now include the PD-1 inhibitor pembrolizumab (Keytruda), which is FDA approved for patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient solid tumors that have progressed after prior treatment and who have no suitable alternative treatment options. The combination of pembrolizumab plus lenvatinib (Lenvima) also is approved for patients who do not have MSI-H or mismatch repair-deficient tumors who are not candidates for curative surgery or radiation and have disease progression following systemic therapy.

“We haven’t focused on the role of sequencing in endometrial cancer much at all,” explained Slomovitz. “It is important that we use the current data we have to plan our future trials to look at how we can determine which sequencing strategy works best. Much of what we are doing currently is based on hypotheticals.”

In an interview with OncologyLive®, Slomovitz, professor and chief of the Division of Gynecologic Oncology at Sylvester Comprehensive Cancer Center, University of Miami Health System, discussed the evolving landscape of endometrial cancer.

Q How is the treatment paradigm for endometrial cancer changing?

Traditionally, we have used radiation, chemotherapy, or hormonal therapy. More recently, we have started to incorporate immunotherapy and other biologic therapies.

However, we don’t know the right way to incorporate those treatments [into the paradigm]. We have to use the evidence we have to make some assumptions because we don’t have head-to-head clinical trials with different sequencing strategies.

Particularly for practicing clinicians, when given the choice of sometimes 5 different options, we need to start focusing on the right treatment to give up front to derive the best outcome in the first-line setting and improve outcomes in subsequent settings.

Q What are the current sequencing strategies?

The [standards of care] have always been chemotherapy and radiation therapy for patients with advanced or recurrent disease. Recently, the results of the GOG-258 trial [NCT00942357] demonstrated that radiation therapy with chemotherapy does not [significantly improve] survival. Holding off on radiation therapy until salvage therapy is needed is 1 potentially effective option.

More recently, we learned that immunotherapies are active in endometrial cancer, depending on the patient’s genetic makeup and tumor classification. For example, pembrolizumab is approved for patients with MSI-H endometrial cancer. For patients who do not have MSI-H disease, the combination of pembrolizumab and lenvatinib is approved.

We know those agents work in the second-line setting, but we need to think about whether we can get better results by giving immunotherapy earlier and following it up with chemotherapy.

Q What is the role of molecular alterations in endometrial cancer?

The data from The Cancer Genome Atlas project defined 4 subgroups of endometrial cancer. We are now learning that different outcomes and different treatment options are associated with those subgroups. Patients who have a [highly] mutated disease profile are more amenable and more likely to respond to immunotherapy.

Furthermore, regarding biologic therapies, I conducted a study looking at mTOR inhibitors in combination with hormonal therapy in endometrial cancer. Particularly in chemotherapy-naive patients, we saw a very high response rate and a longer progression-free survival [with that combination]. Perhaps we should be giving patients biologic therapies to take advantage of the high response rate and prolonged progression-free survival and save chemotherapy for later on in a patient’s disease course.

Q What are the main factors that affect treatment decisions?

We have to look at the toxicity profiles of the different agents that we are proposing to give. Obviously, chemotherapy [has a lot of toxicities associated with it], so moving away from chemotherapy would benefit patients.

Especially now, given the era of the coronavirus disease 2019 and social distancing, we are looking to do whatever we can to keep patients out of the hospital. For example, oral therapies, including hormonal therapies, are very exciting. We need to consider that an otherwise healthy, elderly woman [is at an increased risk for the coronavirus disease 2019], and we should try to keep her out of the hospital.

Q What research efforts could have an impact on sequencing?

The LEAP-001 trial [NCT03884101] is looking at the combination of pembrolizumab and lenvatinib versus chemotherapy as first-line treatment in endometrial cancer. That will be a telling, and perhaps a game-changing trial. We need to continue with the clinical trials we are doing. Whether we are in academic- or community-based settings, it is important to participate in clinical trials as best as we can.

We [Gynecologic Oncology Group] are running 2 trials. One is called the RUBY trial [NCT03981796], looking at the combination of chemotherapy with or without the [PD-1-directed checkpoint inhibitor dostar]limab [TSR-042]. The other is the DUO-E trial [NCT04269200], which is evaluating chemotherapy in combination with durvalumab [Imfinzi] with or without the PARP inhibitor olaparib [Lynparza] as maintenance therapy in advanced or recurrent disease.

It is an exciting time to participate in clinical trials. I would encourage [my colleagues] to consider opening up clinical trials to their patients.
When treating non-metastatic castration-resistant prostate cancer (nmCRPC),

**METASTASIS-FREE SURVIVAL IS JUST THE HALF OF IT**

**INDICATION**
NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

**IMPORTANT SAFETY INFORMATION**

**Embryo-Fetal Toxicity:** Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

**Adverse Reactions**
Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%).

Clinically significant adverse reactions occurring in ≥ 2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs. 3.4% on placebo) and heart failure (2.1% vs. 0.9% on placebo).

**Drug Interactions**

Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA...
NUBEQA®—Focus on both MFS and tolerability\textsuperscript{1,2}

More than double the median MFS with NUBEQA + ADT\textsuperscript{*} vs 18 months with ADT alone\textsuperscript{1}  
\[ (HR: 0.41, 95\% CI: 0.34-0.50, \ P<0.0001) \] \textsuperscript{*95\% CI: 34.3-NR. 95\% CI: 15.5-22.3.}

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16\% vs 11\%), pain in extremity (6\% vs 3\%), and rash (3\% vs 1\%)\textsuperscript{‡}

9\% of men permanently discontinued due to adverse reactions whether on NUBEQA + ADT or ADT alone

Dose interruptions and reductions due to adverse reactions occurred in 13\% and 6\%, respectively, of patients treated with NUBEQA + ADT.\textsuperscript{1} The most frequent reasons for permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4\%) and death (0.4\%). The most frequent reasons for dose interruptions included hypertension (0.6\%), diarrhea (0.5\%), and pneumonia (0.5\%). The most frequent reasons for dose reductions included fatigue (0.7\%), hypertension (0.3\%), and nausea (0.3\%).\textsuperscript{1}

NUBEQA®—proven to extend MFS, now with statistically significant OS\textsuperscript{1,3}

31\% reduction in the risk of death with NUBEQA + ADT compared to ADT alone\textsuperscript{3}

Metastasis-free survival (MFS) was the primary endpoint. Overall survival (OS) was a key secondary endpoint. OS data were not mature at time of first analysis (5\% of the required number of events). At final analysis, OS was statistically significant but median not reached. \[ HR: 0.69 (95\% CI: 0.53-0.88); \ P<0.003. \]

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study [ARAMIS] in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1309 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BCRP-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, \textsuperscript{1}\textsuperscript{*10\%} bone scan by BICR, unacceptable toxicity, or withdrawal. \textsuperscript{1,2}

\textsuperscript{1}All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20\% vs 9\%), increased aspartate aminotransferase (23\% vs 14\%), and increased bilirubin (16\% vs 7\%). Grade 3-4 for same lab abnormalities were, respectively, 4\% vs 0.6\%, 0.5\% vs 0.2\%, and 0.1\% vs 0.7\%.

\textsuperscript{*}The NUBEQA Free Trial Program provides 2 months’ supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions, please call DUDE Access Services at 1-833-337-8333 or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions.
NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019
BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1)].

6 ADVERSE REACTIONS
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.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on NUBEQA
Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Table 2: Laboratory Test Abnormalities in ARAMIS

Table 1: Adverse Reactions in ARAMIS

Table 2: Laboratory Test Abnormalities in ARAMIS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
The safety and efficacy of NUBEQA have not been established in pregnant females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)].

8.2 Lactation
Risk Summary
The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential
Contraception
Males
Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1)].

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

8.5 Geriatric Use
Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment
Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m2) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m2). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m2) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment
Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment.

10 OVERDOSAGE
There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hypospermia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION
Dosage and Administration
Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity
Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

Infertility
Advise male patients that NUBEQA may impair fertility [see Use in Specific Populations (8.3)].

Oral Oncolytics Will Require Health Care System to Adapt

by MARK ALWARDT; BEN JONES; AND VALERIE A. RUSSO, PharmD

JUDGING FROM THE DRUG PIPELINE, the future of oncology is oral chemotherapy. These agents make up 25% to 35% of oncology drugs in development. It’s clear that in 5 to 10 years, oral therapies likely will be a much larger component of potential treatment plans for patients with cancer.

The question is: How will our health care system adapt to this shifting paradigm? Although most intravenous (IV) cancer treatments are covered under the medical component of health insurance plans, oral oncolytics typically fall under the prescription drug component, which often results in a considerable disparity in cost.

For Medicare patients, IV therapies are covered under Part B benefits; however, oral cancer drugs are generally covered by Medicare Part D. Under the Affordable Care Act, the Medicare Part D benefit now includes coverage in the coverage gap, known as the donut hole.

Patients continue to have challenges with medication access because of out-of-pocket expenses. The cost for new oral cancer drugs is in the range of $10,000 per month. Payers are shifting management of these drugs to their pharmacy benefit managers (PBMs), and PBMs further control costs by limiting dispensing through specific specialty/mail order pharmacies. PBMs also place oral cancer drugs into cost-sharing tiers with variable co-pay expectations for patients.

Overall, more of the cost burden of cancer care is being shifted to patients. The percentage of patients with cancer unable to access their therapies due to cost is expected to increase over the next 10 years (TABLE).3

Addressing the insurance and payer coverage of oral oncology medications and ensuring patient access has been a priority of many organizations.

For example, the Community Oncology Alliance recently issued a position statement that supports the passage of an oral parity law on the federal level, a central theme being the need for more comprehensive protection than what state laws can provide.4

So far, to protect patients, 43 states have passed oral parity laws, which are designed to ensure that oral cancer therapies are no less affordable than their injectable counterparts. These laws differ significantly from state to state.3

For example, some state laws pertain only to health care plans that are state regulated. Additionally, states achieve parity in slightly different ways, leaving millions of Americans with non–state-regulated plans unprotected.

Passing the Cancer Drug Parity Act of 2019, a bill introduced in the US House of Representatives in March 2019, would ensure that patients can expect to face the same cost-sharing model for oral cancer-fighting pills that they do for IV therapies.

Activity on this bill, however, appears to be on hold because of the coronavirus disease 2019 pandemic.

THE RISE OF ORAL ONCOLYTICS

Oral cancer-fighting medications are not entirely new. Molecular targeted therapies,
such as tamoxifen for hormone-receptor positive breast cancer, have been around for more than 40 years. A record number of oncology drugs launched in 2018, bringing new options to patients and continuing the transformation of treatment patterns occurring from the introduction of immunotherapies less than 5 years ago. These new drugs use diverse mechanisms to treat cancer and include 3 immuno-oncology therapies. Over half of the new therapies are delivered as an oral formulation, have an orphan indication, or include a predictive biomarker on their label.

Additionally, in 2019, the FDA’s Center for Drug Evaluation and Research approved 11 new novel therapies for oncology; 8 were oral oncolytics. Although oral therapies are not adverse event (AE) free, many formulations allow for a better quality of life and fewer AEs, such as the hair loss and high toxicity that come with systemic chemotherapy.

Uncertainty remains regarding the use of oral oncology agents. For example, how do we make sure patients adhere to treatment regimens? Oncology providers, and community practices in particular, must take a leading role in evolving and adapting to ensure the full benefit and potential of oral chemotherapeutic agents are realized in the patient experience.

Patient access to therapies is another area of deep concern, because a disparity of cost share between orals and injectables can directly affect quality of care. Treatment decisions and options are dependent on drug coverage, and a higher cost share for oral drugs could push patients toward less effective therapies. This is not a question of brand versus generic drugs, because oral drugs present a different therapy pathway.

Leaving patients vulnerable to financial toxicity can have a negative effect on health outcomes and add burden to practices that dedicate staff, and therefore cost, to work on the patient’s behalf to find financial assistance through discount programs and charitable organizations. Clearly, the insurance cost share should be the same whether a therapy is administered orally or intravenously. What matters is that the therapy is medically necessary and that the patient receives the safest and most effective therapy available for their diagnosis.

WAVES OF NEW LEGISLATION

The move toward oral parity is also in line with a growing trend toward passing legislation, on both the federal and state level, that is designed to reduce the cost of all prescription drugs. Americans spend more on pharmaceuticals than ever before; health spending and prescription drug price growth are expected to surpass that of the gross domestic product.

This mounting crisis has resulted in some significant congressional actions and proposals on drug pricing, many of which have bipartisan support. Congress has closed the Medicare Part D donut hole, requiring pharma manufacturers to pay 70% of the brand name drug costs for beneficiaries in the coverage gap. Legislation has also been passed to repeal “gag orders,” banning contracts that don’t allow pharmacists to tell patients how they could pay less for medicine.

National health spending is projected to grow at an average annual rate of 5.4% for 2019-2028 and reach $6.2 trillion by 2028. Among major payers, Medicare is expected to experience the fastest spending growth (7.6% per year over 2019-2028), largely as a result of having the highest projected enrollment growth.

Additionally, the insured share of the population is expected to fall from 90.6% in 2018 to 89.4% by 2028. Currently, both the Senate and House are considering reduced out-of-pocket maximum proposals for Medicare Part D.

There is also consensus around passing a federal bill that would protect patients from “surprise medical billing” from out-of-network providers, such as when a patient cannot choose the emergency department, physicians, or ambulance provider.

The White House under President Trump has proposed the American Patients First drug pricing blueprint to reduce the cost of prescription drugs. The US Department of Health and Human Services has gone so far as to propose a model that is fraught with unintended consequences, all in the name of setting certain drug prices based on an international benchmark.

These are big steps, and they’re being taken with the patient in mind, with the sole intent of lowering out-of-pocket costs. Policy makers may have differing opinions on how to get there, but all are reaching for the same end goal: to reduce the cost burden of prescription drugs on consumers.

When it comes to cancer care, treatment pathways are undergoing a sea change as targeted oral therapies replace systemic, injectable chemotherapies. In 5 to 10 years, IV therapies may no longer be an option for certain cancers.

Our health care system needs to adapt accordingly, because we can’t have a system that puts patients at a disadvantage. Addressing this issue now is a necessary next step to keeping the system equitable and putting the patient first.

Mark Alwardt is vice president of specialty pharmacy at Biologics by McKesson; Ben Jones is vice president of government relations and public policy at Biologics by McKesson; and Valerie A. Russo, PharmD, is director of in-office dispensing operations at Biologics by McKesson.

For a full list of references, see the article at OncLive.com.
How Social Determinants of Health Affect Patient Outcomes

by BRUCE FEINBERG, DO

OVER THE PAST DECADE, a growing body of clinical evidence has shown that social determinants of health (SDOH)—the conditions in which people are born, grow, live, work, and age, as defined by the World Health Organization (WHO)—can be as important to a patient’s outcomes as their genetics. Factors such as financial security, food security, social isolation, housing security, addiction, access to transportation, and health literacy impact all aspects of a patient’s care.

This is especially true in cancer treatment. More than 90% of oncologists said social determinants of health significantly impact outcomes for patients with cancer, according to research by Cardinal Health Specialty Solutions. The findings are based on surveys of 160 US oncologists from a mix of community- and hospital-based practices conducted February 2020 to April 2020. It’s the latest in an ongoing series of reports designed to help physicians, manufacturers, and other health care stakeholders understand trends and changes impacting specialty medicine.

Two-thirds (68%) of participating oncologists said at least half of their patients are negatively impacted by SDOH. When asked what barriers have the most significant impact on patients, oncologists noted financial insecurity/lack of health insurance (83%), followed by access to transportation (58%), health literacy (53%), and social isolation (43%).

Notably, the survey was designed, and most of the responses were received, before the onset of the coronavirus disease 2019 (COVID-19) pandemic in the United States. The SDOH issues uncovered in the research have become even more relevant in the face of the current health care crisis. Those who lack financial security, education, employment, or housing are at greater risk of being infected with the virus and may not be able to access appropriate medical care. In some cases, eg, patients with cancer, these disparities have led to higher mortality rates.

THE NEED FOR MORE RESOURCES

In recent years, the United States has seen a shift toward greater awareness around the importance of SDOH and a more comprehensive approach to health care. Medicare Advantage Plans have been authorized to cover nonmedical benefits, and some large commercial payers are making investments to help patients with food, transportation, and housing.

Yet the survey findings indicate oncologists see the need for more resources. Nearly 70% of participating oncologists said they often or always discuss social determinants with their patients. However, 81% acknowledged that they and their staff were time constrained in their ability to adequately address those same topics.

Participating oncologists assigned responsibility for assistance programs across the players in the health care space, including government, nonprofits, commercial payers, hospitals, and pharmaceutical manufacturers. Oncologists said assistance was most needed in three areas: cost of medicine (79%), transportation (57%), and tools to improve patient understanding of disease and treatment (29%)—yet a strong majority (76%) said that assistance programs are not readily accessible.

The survey clearly shows that social factors are critically important to patient outcomes. There is, however, no simple solution, and oncologists believe that everyone in the health care system must play a role in finding the answers. As the COVID-19 pandemic continues to unfold, along with its economic impacts, these issues will remain critical in the months and years ahead.

REFERENCE

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CAR T Pioneers Describe Challenges

by RENIER J. BRENTJENS, MD, PhD; AND MANJUSHA NAMUDURI, MD

This is part 1 in a series courtesy of Memorial Sloan Kettering Cancer Center. Look for part 2 in the next issue of OncologyLive®.

ADVANCES OF CHIMERIC ANTIGEN receptor (CAR) T-cell therapy technologies are in rapid development and under investigation in a range of preclinical and clinical research around the globe. In a paper recently published in Expert Review of Hematology, we reviewed the main challenges with current CD19-targeted CAR, obstacles to adopting CAR T-cell therapy in solid tumors, and various strategies that scientists are pursuing to overcome these issues.1

This update is the first in a 2-part series that provides an overview of antigen escape, T-cell persistence, safety when using CARs in hematologic malignancies within and beyond the setting of B-cell acute lymphoblastic leukemia (B-ALL), and the range of different strategies under investigation to address these issues.

Scientists at Memorial Sloan Kettering Cancer Center (MSK) pioneered CAR T-cell therapy as a treatment for cancer and were the first to demonstrate that CD19 was a robust target. We continue to explore new ways to advance CAR T cells as a treatment for other hematologic cancers, including lymphoma and multiple myeloma, as well as extending their use to solid tumors, including breast cancer, ovarian cancer, lung cancer, and mesothelioma.

THE EVOLUTION OF CAR T-CELL THERAPY

CARs are genetically engineered receptors on T cells that include an HLA-independent antigen recognition domain, usually in the form of a single-chain Fv (scFv) from an antibody, combined with a T-cell activation domain.2 Once activated, CAR T cells become cytotoxic against the target antigen.

First-, second-, and third-generation CAR receptors have 0, 1, or 2 costimulatory domains, respectively. Newer generations, known as armored CARs, also deliver cytokines or PD-1-blocking scFvs, which enhance antitumor activity. Despite the high response rates of 80% to 90% achieved with CD19-targeted second-generation CAR T cells in treating B-ALL,3,4 they have not had comparable responses in other CD19-positive hematologic cancers or solid tumors.

ANTIGEN ESCAPE

An epitope is the specific segment of a protein to which the antibody binds. Data have demonstrated the target epitope loss in patients with B-ALL who lose durability of remission after treatment with CD19-directed CARs.5 Other research suggests that epitope loss may be secondary to deletions, mutations, and alternative splicing of the CD19 antigen recognition domain, allowing tumor cells to escape recognition.6

CD19 epitope loss has also led to the emergence of a myeloid clone after treatment for mixed-lineage leukemia-rearranged B-ALL in disease recurrence.7 Interestingly, antigen loss has also been observed in lymphoma8 and chronic lymphocytic leukemia9 with CAR T-cell therapy.

Preclinical models have shown that a process called trogocytosis may play a role in antigen escape with both CD28- and 4-1BB–based CARs. Trogocytosis is an active process that tumors use to transfer the target antigen onto T cells so they can escape destruction. Scientists believe this is reversible, but it has yet to be demonstrated in humans.10

One solution to overcome antigen escape is to combine single-target CARs that address different targets as a pooled product or use dual CARs11-13 or tandem CARs.14 Clinical trials are currently testing these combination approaches (TABLE). Another approach under investigation is low-dose radiation to sensitize antigen-negative tumor cells to CAR T cells and induce their death through the tumor necrosis factor–related apoptosis-inducing ligand.15

T-CELL PERSISTENCE

The oncology community has yet to reach a consensus on the optimal duration of persistence for maintaining long-term remission with CAR T-cell therapy. Investigators have observed comparable response rates with a median duration of persistence of 14 days16 and 168 days.17 Still, relapses have been observed in some cases in which CARs were no longer performing immunosurveillance.8

T-cell stimulation is a double-edged sword: It increases persistence, but overstimulation can result in exhaustion.20 Some research has demonstrated that longevity can be improved without compromising efficacy by eliminating a signaling redundancy or by placing immunoreceptor tyrosine-based activation motifs near the membrane.21 A well-studied explanation for decreased persistence of CAR T cells is transgenic immune responses against scFv of murine origin.22-24 A fully human scFv-based CAR has shown promising activity against the target antigen in preclinical research.25 Human scFv-based CARs may be possible as a salvage therapy against the same antigen in patients treated with murine-scFv CARs, as demonstrated in a study among patients with B-ALL.26 Clinical trials using humanized as well as fully human scFv-based CARs are in progress (TABLE).

Several groups have studied central memory27-28 and stem cell memory T cells29-32 to learn more about persistence.
mechanisms in adoptive cell therapy—for example, CARs. Approaches using defined ratios of CD4:CD8 T cells revealed that the CD4 subset is vital for boosting overall antitumor activity. Several clinical trials are ongoing in this area, including 1 study investigating humanized CARs and 2 studies using fully human scFv-based CARs (TABLE).

Investigators have achieved persistence and reduced exhaustion in CAR T cells by optimizing the ratio of CD4:CD8 cells through alterations to signaling domains and pathways. Another promising design modification involved diminishing redundant signaling, which improved effector and memory cell ratios and CAR persistence.

An alternative approach to improving persistence involves stimulating the T-cell receptor using antigens from viruses, such as the Epstein-Barr virus or cytomegalovirus, and then using the cytotoxic T cells to transduce CARs. Current clinical trials testing this approach with hematologic and solid tumor antigen-directed CARs include NCT0085930, NCT01109095, NCT03768310, NCT01460901, and NCT01953900.

Finally, tumor vaccines and antigen-presenting cells may provide an immunological boost to CAR efficacy and persistence, and investigators are evaluating these in clinical trials NCT01953900, NCT02482532, NCT03186118.

**SAFETY**

One of the biggest challenges with CART-cell therapy is the potential for toxicity, as healthy cells may express the same targets as cancer cells. Cell engineers are incorporating “off” and “on” switches and employing other strategies to mitigate toxicity.

CARs with off switches, also called suicide genes, can be rapidly destroyed when toxicities arise or after they have eliminated cancer cells. Study data have recently shown that dasatinib (Sprycel) can pause CAR T-cell activity temporarily, acting as a reversible switch. Current trials investigating the safety of off switches include NCT02414269, NCT03696784, NCT03500991, NCT02311621, and NCT03016377. Other strategies for inactivating CARs involve checkpoint blockade, titrating activation with an antibody switch, and using self-limiting or transient strategies to mitigate toxicity.

Beyond safety switches, scientists are investigating ways to reduce toxicities without compromising efficacy. For example, one strategy is the prophylactic administration of tocilizumab (Actemra), an IL-6—blocking antibody (NCT02906371), or an IL-1 antagonist. Emerging evidence in the setting of CD19-directed CARs for B-ALL shows that the severity of CRS depends on tumor burden. Therefore, strategies to reduce the risk of CRS include optimizing patient selection, changing the conditioning regimen, and using a split-dose approach for CAR T-cell infusion.

**TABLE. Select CAR Strategies Under Investigation**

<table>
<thead>
<tr>
<th>Therapeutic intervention</th>
<th>Clinical trial description (ClinicalTrials.gov identifier) (N = target enrollment)</th>
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</thead>
<tbody>
<tr>
<td><strong>Combination CAR approaches</strong></td>
<td></td>
</tr>
<tr>
<td>Patient-derived CD19-specific CAR also expressing HER21 and CD22-specific CAR T cells also expressing an EGFr</td>
<td>Phase 1 (NCT03330691): patients aged 12 months to 26 years with CD19+ leukemia (N = 33)</td>
</tr>
<tr>
<td>CD19-CD22 CAR T cells with chemotherapy</td>
<td>Phase 1 (NCT03241940): patients aged 1-30 years with recurrent refractory B-cell malignancies (N = 50)</td>
</tr>
<tr>
<td>Cyclophosphamide and fludarabine followed by CD19-CD22 CAR T cells</td>
<td>Phase 1/2 (NCT04029038): patients aged 6 months to 70 years with advanced CD19+, CD22+ lymphoid malignancies (N = 30)</td>
</tr>
<tr>
<td><strong>Humanized or scFv-based CARs</strong></td>
<td></td>
</tr>
<tr>
<td>Humanized CD19-directed autologous T cells</td>
<td>Phase 1 (NCT02374333): patients aged 1-24 years with relapsed or refractory CD19+ leukemia and lymphoma previously treated with cell therapy (N = 85)</td>
</tr>
<tr>
<td>A 1:1 mixture of CD4:CD8 autologous T-cells lentivirally transduced to express a second generation 4-1BB human CD19-specific CAR and HER21G</td>
<td>Phase 1/2 (NCT03684889): patients aged 1-28 years with CD19+ leukemia or lymphoma (N = 112)</td>
</tr>
<tr>
<td>Cyclophosphamide with anti-BCMA CAR T cells followed by fludarabine</td>
<td>Phase 1 (NCT03602612): adults aged 18-73 years with multiple myeloma (N = 42)</td>
</tr>
<tr>
<td><strong>Using defined ratios of CD4:CD8 T cells</strong></td>
<td></td>
</tr>
<tr>
<td>Autologous HER21(EQ)IIB/CD191+ TCM cells via intratumoral/intracavitary catheter</td>
<td>Phase 1 (NCT03889230): adults aged 18-75 years with recurrent refractory malignant glioma (N = 42)</td>
</tr>
<tr>
<td>Anti-CD19 CAR lentiviral vector-transduced autologous T cells with durvalumab</td>
<td>Phase 1 (NCT02706405): adults ≥ 18 years with relapsed or refractory B-cell non-Hodgkin lymphoma (N = 42)</td>
</tr>
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</table>

**ADVANCING INNOVATION**

At MSK, we are dedicated to finding new ways to improve patient outcomes through groundbreaking preclinical and clinical research. We are currently conducting 15 clinical trials testing CAR T-cell therapy in a range of indications, including lymphomas, multiple myeloma, advanced breast cancer, mesothelioma, and lung cancer.

The paper was not funded. Namuduri is an ad hoc consultant for Cellectar Biosciences. Brentjens receives royalties and grant support from Juno Therapeutics and is a consultant for Juno/Celgene. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
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CLR 131 Leads a New Generation of Lipid-Based Cancer Drug Delivery Systems

by JANE DE LARTIGUE, PhD

**A NOVEL COMPOUND** that uses abundant lipids in cancer cell membranes to deliver a radioisotope to the tumor environment shows early signs of efficacy in a range of B-cell malignancies, including multiple myeloma.1,2

CLR 131 is a phospholipid-drug conjugate (PDC) designed to provide a payload of iodine-131 directly to the cytosol and cytoplasm of tumor cells.² Cellectar Biosciences, a biopharmaceutical company based in Florham Park, New Jersey, is investigating the potential of CLR 131 in hematologic and solid tumors. The company also is exploring its PDC approach as a platform technology for other oncologic conjugates.⁴

Positive clinical trial data have been announced for patients with B-cell malignancies,² including multiple myeloma, and CLR 131 has secured fast track designation from the FDA for 3 separate indications.⁵,⁶ If it lives up to its potential, CLR 131 could be the first of many such drugs from Cellectar, with other payloads being explored.¹

Meanwhile, the underlying technology shines a light on the broader use of lipids as vehicles for cancer therapies. With the advent of nanotechnology in medicine, lipid-based carriers have been designed to encapsulate drugs to improve delivery to the tumor site, in the hopes of reducing generalized toxicity and improving therapeutic effect.⁸⁻¹⁰

Several FDA-approved liposomal formulations of common chemotherapy drugs are on the market.¹¹ Ongoing clinical efforts aim to improve the efficacy of some of these drugs; notably, daunorubicin plus cytarabine (CPX-351; Vyxeos)¹² and liposomal irinotecan (Onivyde).¹³ CPX-351 was initially approved in 2017 in acute myeloid leukemia settings and Onivyde was cleared in 2015 for progressive metastatic pancreatic adenocarcinoma.

Additionally, newer lipid-based strategies aimed at overcoming the challenges of liposomal formulations are in development. These include SB05-EndoTAG-1 (SynCore Biotechnology), which combines paclitaxel with lipids¹⁴; mRNA-2416 (Moderna), which encodes OX40L in a lipid nanoparticle¹⁵; and Promitil (LipoMedix), a lipid-based form of mitomycin-C.¹⁶

**IMPROVING DRUG DELIVERY**

Investigators have long sought more specific cancer drugs with reduced off-target toxicity and enhanced therapeutic efficacy. The development of molecularly targeted therapies has been one result, but new drug delivery systems may achieve similar goals. Thanks to the advent of nanotechnology, significant advances in the development of drug carrier technologies for cancer therapy have occurred in the past several decades.⁸⁻¹⁰

Broadly speaking, drug carriers are designed to shield drugs from interaction with healthy cells and facilitate accumulation at the tumor site. The latter is believed to occur as a result of the enhanced permeability and retention effect. Nanoparticles are too big to readily pass through the normal vasculature into healthy tissues but not the abnormal, leaky blood vessels characteristic of the tumor microenvironment. The lack of lymphatic drainage from tumor vessels adds to this effect.¹⁷

Nanoparticles prepared from natural polymers, such as lipids, proteins, and peptides, represent the most promising approach. In particular, liposomes are the most extensively studied type of nanoparticle drug carrier and account for first generation of FDA-approved lipid-based drug delivery systems.¹⁸

Liposomes are spherical vesicles composed of 1 or more phospholipid bilayers surrounding an aqueous core. Depending on its properties, a drug can be encapsulated within the core (a hydrophilic drug) or held in the bilayer (a hydrophobic drug) (FIGURE 1).³⁻¹¹

Among their advantages over naked drugs, liposomes and other lipid-based delivery systems can reduce toxicity, prolong half-life in the circulation, and improve pharmacokinetics. Additionally, because of their biocompatibility with cell membranes, they are more readily taken up into cells via endocytosis. Because the drug remains behind a lipid barrier once inside the cell, being released only upon lysosomal degradation, it may avoid eviction from the cell by transporter pumps that play a large role in drug resistance.⁹,¹¹,¹⁹

**LIPOSOMAL CARRIERS**

**Chemotherapy Delivery**

Beginning with the 1995 approval of doxorubicin hydrochloride liposome injection (Doxil) for the treatment of AIDS-related Kaposi sarcoma and, subsequently, multiple myeloma and ovarian cancer, several

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**FIGURE 1. Exploiting the Cell Membrane⁶,¹¹**

Lipid-based drug delivery systems are designed to leverage phospholipid bilayers in the cell membrane. A drug can be encapsulated within the liposome’s core (hydrophilic drugs) or held in the bilayer (hydrophobic drugs).
liposomal formulations of conventional chemotherapies have become available. Despite better developed drug properties, some approved liposomal formulations only moderately improved patient survival compared with conventional chemotherapy. Their development revealed a number of inherent challenges. Early on, investigators discovered that liposomes were rapidly recognized and engulfed by macrophages, which led to their destruction by the mononuclear phagocyte system.

Nevertheless, ongoing clinical development has demonstrated greater efficacy for several of these compounds. CPX-351 continued to show an overall survival (OS) benefit versus conventional 7 + 3 chemotherapy for patients with newly diagnosed high-risk/secondary acute myeloid leukemia in findings from a phase 3 trial (NCT01696084) presented at the 2020 European Hematology Association Virtual Congress.

After a median follow-up of 60.65 months, the median OS was 9.33 months (95% CI, 6.37-11.86) and 5.95 months with CPX-351 and 7 + 3, respectively (HR, 0.70; 95% CI, 0.55-0.91). The estimated 3- and 5-year OS rates were also higher with CPX-351 versus 7 + 3, at 21% versus 9% and 18% versus 8%, respectively.

The combination of Olivyde plus fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) demonstrated promising outcomes as a frontline treatment for patients with locally advanced or metastatic pancreatic ductal adenocarcinoma. Findings from a phase 1/2 study (NCT02551991) for 32 patients were presented at the European Society of Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer 2020.

The NALIRIFOX regimen resulted in a median progression-free survival of 9.2 months (95% CI, 7.69-11.96) and a median OS of 12.6 months (95% CI, 8.74-18.69). The overall response was 34.4% (95% CI, 18.6%-53.2%), consisting of 1 complete response (CR) and 10 partial responses (PRs). An international, randomized phase 3 trial (NAPOLI 3; NCT04083235) exploring the use of frontline NALIRIFOX compared with gemcitabine and nab-paclitaxel (Abraxane) in patients with metastatic pancreatic cancer is now under way.

Other Payloads
Besides chemotherapy, other cancer drugs can be contained within liposomes. Nucleic acid-based drugs, which include oligodeoxynucleotides, plasmid DNA, short interfering RNA, and messenger RNA (mRNA), can be used for gene therapy. However, the use of naked genetic material is challenging due to its large size, instability in the circulation, and susceptibility to degradation by nucleases. Lipid-based carriers offer a way to address these issues.

Bio-Path Holdings is developing prexigebersen (BP1001), BP1002, and BP1003; the latter is still in preclinical testing. All 3 are liposome-encapsulated antisense oligonucleotides that inhibit synthesis of the GRB2, BCL2, and STAT3 proteins, respectively. Prexigebersen is most advanced in clinical development; Bio-Path recently announced an updated interim analysis of stage 1 of an ongoing phase 2 study in AML (NCT02781883).

Among 17 evaluable patients treated with a combination of prexigebersen and low-dose cytarabine (LDAC), 11 had a response, including 5 CRs. Moving forward, patients in stage 2 of the trial will be treated with a combination of prexigebersen, decitabine, and venetoclax, instead of LDAC, following initial safety testing of this combination in which 3 of 6 patients had a response.

All the currently approved liposomal formulations rely on passive targeting of the tumor tissue through enhanced permeability and retention. However, the irregular tumor vasculature thought to be responsible for this effect can also work against effective drug delivery, as can the elevated fluid pressure surrounding the tumor.

To further enhance active tumor-targeted drug delivery, development of functionalized liposomes has also been explored, in which properties of the liposome are engineered for improvements. This includes altering the type of lipid to affect the size or charge of the liposome or conjugating other drugs to the liposome surface. Immunoliposomes, for example, are generated by chemically coupling liposomes with antibodies or antibody fragments against cancer cell-specific antigens, such as EGFR.

SB05-EndoTAG-1 encapsulates paclitaxel in positively charged liposomes. These are designed to interact with the negatively charged endothelial cells of newly formed blood vessels, releasing paclitaxel into these cells, killing them, and cutting off the tumor’s blood supply. Phase 3 trials are ongoing in locally advanced/metastatic pancreatic cancer (NCT03126435) and triple-negative breast cancer (NCT03002103).

**LIPID-DRUG CONJUGATES**
Other types of lipid-based drug delivery

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**FIGURE 2. Design of Novel Phospholipid-Drug Conjugate**

[Diagram of Phospholipid-Drug Conjugate]

Phospholipid-drug conjugates (PDCs) designed by Cellectar Biosciences use phospholipid ethers and chemical linkers to deliver targeted anticancer drugs.

- **Phospholipid ether** (Cancer-targeting vehicle)
- **Linker**
- **Drug**
- **PDC**

Phospholipid-drug conjugates (PDCs) designed by Cellectar Biosciences use phospholipid ethers and chemical linkers to deliver targeted anticancer drugs.
systems, beyond lysosomes, come with advantages and disadvantages. There are several major types of lipid nanoparticles; the lipid core may be solid, liquid, or both, and the core may contain single or multiple compartments of drug, among other distinctive features.8,19

Moderna Therapeutics is developing 2 lipid nanoparticle-based encapsulation systems that contain synthetic mRNAs encoding immunostimulatory proteins.27 Results from an ongoing study of mRNA-2416 (NCT03323398), in which the encapsulated mRNA encodes OX40L, were presented at the 2020 American Association for Cancer Research Virtual Meeting I. Despite being well tolerated, mRNA-2416 had modest antitumor activity, but it is hoped that this may be enhanced by combining it with durvalumab (Imfinzi), a PD-L1 inhibitor. This combination is being evaluated in part B of the study.35

Lipid-drug conjugates (LDCs), in which cancer drugs are linked with lipid molecules, are among the most promising types of lipid nanoparticle. LDCs also can facilitate the loading of hydrophobic drugs into other lipid-based carrier systems.8,28

Promitil is an LDC involving mitomycin-C that is further encapsulated in a pegylated liposomal carrier.16 In a phase 1a dose-escalation study, toxicity was lower and dose tolerability higher than historical data for “naked” mitomycin-C. In the phase 1b portion of the trial in patients with advanced, chemorefractory colorectal cancer, Promitil was evaluated alone or combined with either capecitabine or capecitabine and bevacizumab (NCT01705002). Among 36 response-evaluable patients, stable disease was observed in 42% at week 12. Median survival was 8.7 months, and adding capecitabine and bevacizumab to Promitil had no further effect. AEs were mostly mild to moderately severe.29

**TARGETING LIPID RAFTS**

Cellectar Biosciences is developing a different kind of LDC. CLR 131 is a PDC, a proprietary mix of phospholipid ethers (PLEs) covalently linked to a cytotoxic radioactive isotope of iodine-131.3

PDCs offer a lipid-based carrier system with a unique feature: They exploit the altered lipid composition of cancer cell membranes to more actively target tumors. PLEs are naturally occurring lipids that are taken up into cells via lipid rafts, cholesterol-rich regions of the plasma membrane that play a key role in cell signaling. PLEs accumulate in cancer cells, in part because their cell membranes contain an enhanced number of lipid rafts.1,10-32

Thus, the lipid rafts on the surface of cancer cells are bound by multiple PDCs via their PLE moiety. When the lipid rafts eventually undergo transmembrane flipping, they deliver the PLEs and their radioactive payload into the cancer cell. Proposed advantages of this system include the PDCs’ ability to gain entry into a wide variety of cancer types and indiscriminately target all cells within a tumor without relying on expression of a specific antigen.1

Furthermore, the technology could offer considerable flexibility in the types of payloads that can be used and could be further refined via linker design (FIGURE 2).1 Cellectar has several other PDCs in preclinical development, including agents designed to produce cell cycle arrest, inhibit protein translation, and disrupt the cytoskeleton.33

CLR 131 has been granted orphan drug status in multiple myeloma, Ewing sarcoma, neuroblastoma, osteosarcoma, rhabdomyosarcoma, and lymphoplasmacytic lymphoma (LPL).34 CLR 131 also has fast track designation for multiple myeloma, diffuse large B-cell lymphoma (DLBCL), and LPL/Waldenström macroglobulinemia (WM).3,5-7

The most recent fast track designation, for LPL/WM, follows positive results from the ongoing phase 2 CLOVER-1 trial (NCT02952508); Cellectar announced that all 4 treated participants with LPL/WM so far achieved an objective response, with 1 achieving CR.27,34

In this trial, patients with relapsed/refractory (R/R) B-cell lymphomas, multiple myeloma, and non-Hodgkin lymphoma (NHL) were treated with 3 doses of CLR 131: less than 50 mCi total body dose (TBD; an intentionally subtherapeutic dose), 50 mCi TBD, and 75 mCi TBD. Patients in both the multiple myeloma and NHL cohorts had a median age of 70 years and were heavily pretreated.34

The overall response rate (ORR) for patients with multiple myeloma (n = 33) was 34.5% across all doses (42.8% at the 75 mCi dose; 26.3%, 50 mCi). In patients with NHL, the ORR among 19 patients was 42% (43%, 75 mCi; 42%, 50 mCi). Subtype assessments demonstrated ORRs of 30% (with 1 CR) in patients with DLBCL and 33% for patients with chronic lymphocytic leukemia, small lymphocytic leukemia, and marginal zone lymphoma. CLR 131 was well tolerated across all dose groups.34

Cellectar simultaneously announced the completion of a phase 1 dose-escalation study of CLR 131 in patients with R/R multiple myeloma (NCT02278315). In this trial, 4 single-dose cohorts were examined (25, 37.5, 50, and 62.5 mCi TBD). The study was modified in 2018 to test fractionated doses (2 doses of 31, 37.5, or 40 mCi TBD, given 1 week apart). For both the single- and fractionated-dose cohorts, CLR 131 was administered as 30-minute intravenous infusions in combination with 40-mg weekly low-dose dexamethasone.34

All patients (n = 17) enrolled in the single-dose cohorts experienced clinical benefit, with 16 participants achieving stable disease. Pooled median OS from the 4 cohorts was 22 months.

Compared with patients administered the highest single dose of CLR 131, the cohort that received the lowest fractionated dose showed better tolerability and safety; despite receiving an 18% higher dose overall, these patients required less supportive care (such as blood transfusions) and had a 50% greater reduction in M protein levels, a surrogate marker of efficacy.34

The next fractionated-dose cohort, which received a total 75 mCi TBD (2 x 37.5 mCi TBD; n = 4), had a 50% PR rate, defined as at least a 50% decrease in M protein from baseline. The remaining 2 patients experienced a minimal response, defined as an M protein decrease between 25% and 49.9%.

The authors concluded that CLR 131 showed a clear dose response, with higher doses producing greater efficacy without unacceptable toxicity.35
INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION

HEMORRHAGE

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage occurred between 13-44%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Please see Brief Summary of Prescribing Information and Important Safety Information for CYRAMZA on subsequent pages.
SELECT IMPORTANT SAFETY INFORMATION

GASTROINTESTINAL PERFORATIONS
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

IMPAIRED WOUND HEALING
- Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 28 days following a major surgical procedure and until the wound is fully healed. Discontinue CYRAMZA in patients who develop wound healing complications that require medical intervention.

Please see Important Safety Information on next page and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
**IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)

**Warnings and Precautions**

**Hemorrhage**
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**Gastrointestinal Perforations**
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- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 28 days following a major surgical procedure and until the wound is fully healed. Discontinue CYRAMZA in patients who develop wound healing complications that require medical intervention.

**Arterial Thromboembolic Events**
- Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 2-3%. Grade 3-5 ATE incidence was 1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

**Hypertension**
- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension occurred between 11-26%. Grade 3-5 hypertension incidence ranged from 4-15%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions**
- Infusion-related reactions (IRR), including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRR included rigors/fibrillae, back pain/shep, chest pain/and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR occurred between <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

**Worsening of Pre-existing Hepatic Impairment**
- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatic encephalopathy, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatic encephalopathy was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

**Posterior Reversible Encephalopathy Syndrome**
- Posterior Reversible Encephalopathy Syndrome (PRES) (also known as Reversible Posterior Leukoencephalopathy Syndrome [PRES/LIS]) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/Vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Confirm the diagnosis of PRES with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

**Proteinuria Including Nephrotic Syndrome**
- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-20%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is >2+ or greater, perform a 24-hour urine collection for protein measurement. Withhold CYRAMZA for urine protein levels that are >2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

**Thyroid Dysfunction**
- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no report of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

**Embryo-Fetal Toxicity**
- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women.
- Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embry-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

**Lactation**
- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

**Most Common Adverse Reactions—CYRAMZA Administered as a Single Agent (REGARD)**
- The most commonly reported adverse reactions (all Grades; Grade 3-4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in REGARD were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 6% vs 0%), and hypotension (6% vs 2%; 3% vs 1%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.6% and the rate of IRR was 0.4%.

**Most Common Adverse Reactions—CYRAMZA Administered in Combination with Paclitaxel (RAINBOW)**
- The most commonly reported adverse reactions (all Grades; Grade ≥3) occurring in ≥5% of patients receiving CYRAMZA with paclitaxel and ≥2% higher than placebo with paclitaxel in RAINBOW were fatigue/asthenia (10% vs 44%; 12% vs 6%), neutropenia (64% vs 37%; 41% vs 19%), diarrhea (12% vs 23%; 4% vs 2%), epistaxis (21% vs 7%; 3% vs 0%), hypertension (25% vs 6%; 15% vs 5%), peripheral edema (22% vs 14%; 2% vs 1%), stomatitis (23% vs 7%; 1% vs 1%), proteinuria (11% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoaalbuminemia (11% vs 5%; 1% vs 0%), and gastrointestinal hemorrhage events (10% vs 4%; 6% vs 2%).
- The most common serious adverse reactions in patients who received CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

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

**REFERENCES**


Lilly

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CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage
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Hypertension
An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension occurred between 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%.

Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Implication-Related Reactions
Impression-related reactions (IRR), including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRR included rigors/tremors, back pain/apsam, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA in which predemedication was recommended or required, the incidence of all Grade IRR occurred between <1-9%. Grade 3-5 IRR incidence was <1%. Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Worsening of Pre-existing Hepatic Impairment
Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepaticorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration. Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepaticorenal syndrome was higher for patients who received CYRAMZA (8%) compared to patients who received placebo (3%).

A Posterior Reversible Encephalopathy Syndrome
Posterior Reversible Encephalopathy Syndrome (PRES) (also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. Confirm the diagnosis of PRES with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome
Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-20%. Grade 3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is ≥2 or greater, perform a 24-hour urine collection for protein measurement. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction
Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

Embryo-Fetal Toxicity
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

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. The data described in the Warnings and Precautions section reflect exposure to CYRAMZA in 1916 patients from five studies: REGARD, RAINBOW, RAISE, REVEL, and REACH-2.

Gastric Cancer
The safety of CYRAMZA was evaluated in REGARD and RAINBOW. Patients in both trials had locally advanced or metastatic gastric cancer (including GEJ adenocarcinoma) and had previously received platinum- or fluoropyrimidine-containing chemotherapy. Patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Both trials excluded patients with uncontrolled hypertension, major surgery within 29 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin. REGARD excluded patients with bilirubin ≥1.5 mg/dL and RAINBOW excluded patients with bilirubin >1.5 times the upper limit of normal (ULN). CYRAMZA Administered as a Single Agent (REGARD)

Patients received either CYRAMZA 8 mg/kg or placebo intravenously every two weeks. Patients randomized to CYRAMZA received a median of 4 doses; the median duration of exposure was 8 weeks and 32 (14% of 236) patients received CYRAMZA for at least six months. The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients versus 8.7% of patients who received placebo.

The most common adverse reactions (all grades) observed in CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. Table 1 provides the frequency and severity of adverse reactions (CTCAE, version 4.0) in REGARD.

| Table 1: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in REGARD |
|-----------|----------|----------|----------|----------|
| Adverse Reactions | CYRAMZA (N=236) | Placebo (N=115) |
| Vascular | |
| Hypertensiona | 16 | 8 | 8 | 3 |
| Gastrointestinal | |
| Diarrhea | 14 | 1 | 9 | 2 |
| Nervous System | |
| Headache | 9 | 0 | 3 | 0 |
| Metabolism and Nutrition | |
| Hyponatremia | 6 | 3 | 2 | 1 |

a Hypertension is a consolidated term.

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).

Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

CYRAMZA Administered in Combination with Paclitaxel (RAINBOW)

Patients received paclitaxel 80 mg/m² on Days 1, 8, and 15 of each 28-day cycle with either CYRAMZA 8 mg/kg or placebo intravenously every two weeks. Patients randomized to CYRAMZA received a median of 9 doses; the median duration of exposure was 18 weeks, and 53 (26% of 327) patients received CYRAMZA for at least six months. The most common serious adverse reactions in patients who received CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors. Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (5%). The most common adverse reactions (all grades) observed were infection (6%), nausea/vomiting (6%), diarrhea (5%), and pyrexia (4%).
in patients who received CYRAMZA with paclitaxel at a rate of ≥30% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia, neutropenia, diarrhea, and epistaxis. Table 2 provides the frequency and severity of adverse reactions (CTCAE, version 4.0) in RAINBOW.

Table 2: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in RAINBOW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CYRAMZA with Paclitaxel (N=327)</th>
<th>Placebo with Paclitaxel (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>≥ Grade 3 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Peripherals edema</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage eventsa,b</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemiaa</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

a Neutropenia, gastrointestinal hemorrhage events, hypertension, proteinuria, and hypalbuminemia are consolidated terms.

b Includes 1 fatal event in the CYRAMZA arm.

Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with the incidences of antibodies to other products may be misleading.

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

In clinical trials, 86/2890 (3%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of CYRAMZA. Because such 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: Thrombotic microangiopathy
- Neoplasms benign, malignant and unspecified: Hemangioma

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman. There are no available data on CYRAMZA use in pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise a pregnant woman of the potential risk to a fetus.

- Infertility
- Females
  - Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA
  - and for 3 months after the last dose.
- Infertility
- Females
  - Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

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

Juvenile Animal Toxicity Data
In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use
Of the 563 CYRAMZA-treated patients in REGARD and RAINBOW, 205 (36%) were 65 and over, while 41 (7%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 1253 patients in REVEL, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA with docetaxel in REVEL, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of REVEL, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years and over was 1.10 (95% CI: 0.89, 1.36).

Of the 529 patients who received CYRAMZA with FOLFIRI in RAISE, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 191 patients who received CYRAMZA in REACH-2, 95 (48%) were 65 years and over, while 37 (19%) were 75 years and over. Overall, no differences in efficacy were observed between these subjects and younger subjects.

Hepatic Impairment
No dose adjustment is recommended for patients with mild (total bilirubin within ULN and aspartate aminotransferase [AST] >ULN) or total bilirubin >1 to 1.5 times ULN and any AST) hepatic impairment. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA.

Additional information can be found at www.cyramza.com

Lactation
Risk Summary
There is no information on the presence of ramucirumab in human milk or its effects on the breastfed child or on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Females and Males of Reproductive Potential

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

Contraception
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman.

Females
- Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA
- and for 3 months after the last dose.

Infertility
- Females
  - Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use
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CYRAMZA® (ramucirumab) injection, for intravenous use

RB-G HCP BS 18NOV2019
Biosimilars Expand Patient Access to Novel Treatments

by CHRISTINA T. LOGUIDICE

BIOSIMILARS EXPAND PATIENT ACCESS TO NOVEL TREATMENTS

By the cutting-edge of biomedical research and are the fastest-growing class of therapeutic products in the United States. By 2024, the global cancer biologics market is expected to reach $87.6 billion, partially driven by the expiration of more than 20 biologic patents by 2023, which is anticipated to lead to a hugely expanded arsenal of biosimilars over the next few years.

Although these more cost-effective biologic medicines enable a greater proportion of patients to gain access to novel life-prolonging or life-saving treatments, incorporating them into US clinical practice has been slow. Studies show that many US clinicians still have a poor understanding of biosimilars and may be wary of them, despite there being more than 10 years of data from Europe showing that these agents have comparable safety and efficacy to their reference biologics.

During an OncLive Peer Exchange, a panel of hematology-oncology experts discussed the emergence of biosimilar use in oncology. They focused on how biosimilars compare with their biologic originators, how they are assessed and approved, and strategies for incorporating them into clinical practice, including hurdles to their use and efforts to expand their use. The panel also briefly discussed some of the currently approved biosimilars that are being used to treat patients with metastatic non–small cell lung cancer (NSCLC) or metastatic HER2-positive breast cancer.

“There is great value in educating physicians about the use of biosimilars in clinical practice,” moderator Adam M. Brufsky, MD, PhD, said. “When providers understand their scientific rationale and justification, they can appropriately convey clinical messages to their patients and potentially help to streamline the process for increased biosimilar adoption.”

BIOSIMILAR VS BIOLOGIC: COMPARISONS AND APPROVAL PROCESS

A 2018 survey-based US study of 77 oncology clinicians, including 52 physicians, 16 pharmacists, and 9 advanced practice providers, showed that 74% (n = 57) of respondents could not satisfactorily define biosimilars. Additionally, 40.3% (n = 31) of respondents considered biosimilars to be the same as generic drugs, showing a lack of understanding of these agents.

“A biosimilar is a new entity that is highly similar to [but not the same as] the original or approved referenced biologic,” panelist Lee S. Schwartzberg, MD, said. “The basic structure is the same, but there are additions created in cells through complex processes, so there may be slight variations from batch to batch. That is different from a generic, where every single molecule will look the same as every other single molecule.”

Although there are slight differences between biosimilars and their reference products, these agents need to show equivalent safety, efficacy, purity, and potency in drug studies to be approved.

A lack of understanding of biosimilars among US clinicians may be partially attributable to these medicines being a recent addition to the treatment armamentarium in this country. Schwartzberg explained that the United States has lagged behind Europe in approving these medications. Whereas the European Medicines Agency (EMA)
approved its first biosimilar in 2006, a recombinant human growth hormone medicine called Omnitrope (biosimilar of somatropin), the FDA did not approve its first biosimilar until almost a decade later in 2015, the oncology drug Zarzio (filaggrastim-sndz). In comparison, the EMA had approved its first filaggrastim biosimilar in 2008.

“The FDA process for approving a biologic is different than that for approving an originator or reference product,” Schwartzberg said. He explained that the process resembles an inverted pyramid, whereas the process for approving a biosimilar resembles a true pyramid (FIGURE). “For a biosimilar, most of the work is done showing the analytic purity and [structural and functional] similarity to the originator, with less work on the clinical process. If you show that the biosimilar is highly similar to the originator product in terms of the way it looks, the product itself, its functional attributes, its pharmacology and its pharmacokinetics, then you can do fewer clinical trials,” he said. This also keeps the costs of biosimilars down because it eliminates the need to conduct expensive large-scale clinical trials. “You’re conducting only 1 large trial, and that suffices for the FDA to approve the biosimilar for the same indication as the originator,” he said. Schwartzberg explained that the rigorous part of the process with biosimilars is quality assurance, when manufacturing standards comparable with those of the reference biologic are established and maintained.

**BIOSIMILARS IN TREATING NSCLC AND BREAST CANCER**

In patients with metastatic NSCLC, 2 bevacizumab biosimilars are currently approved in the United States: Mvasi (bevacizumab-awwb), approved in 2017, and Ziraveg (bevacizumab-bvzr), approved in 2019. Both are indicated for use in combination with carboplatin and paclitaxel in chemotherapy-naïve patients. These agents are also approved for several other indications, including metastatic colorectal cancer, recurrent glioblastoma, metastatic renal cell carcinoma, and persistent, recurrent, or metastatic cervical cancer. On March 9, 2020, the FDA also accepted a biologics license application (BLA) by Mylan and Biocion Biologics for MYL-14020, another bevacizumab biosimilar, for review under the 351(k) pathway. The companies are seeking approval for the same indications as both of the approved bevacizumab biosimilars have. The FDA decision goal date, as set under the Biosimilar User Fee Act, is December 27, 2020.

For patients with HER2-positive breast cancer, the FDA has approved 5 trastuzumab biosimilars: Ogivri (trastuzumab-dkst), approved 2017; Herzyma (trastuzumab-pkrb), approved 2018; and Kanjinti (trastuzumab-ab-anbs), Ontruzant (trastuzumab-dttb), and Trazimera (trastuzumab-gyyp), approved in 2019. All 5 agents are also indicated for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Despite their being approved, some for several years, not all the agents may be available, Schwartzberg said. “[This has] to do with operational issues at the manufacturers’ level and lawsuits and other things among the originators,” he explained, noting that when trastuzumab biosimilars first became available, his clinic started by offering Kanjinti because it was the first one that came to market.

Regardless, Schwartzberg said that he would feel comfortable using any of the trastuzumab biosimilars. “I believe in the process of approval. I believe that all of the boxes have been checked, and I can feel comfortable that if I use a biosimilar trastuzumab it will work the same way as the originator trastuzumab did,” he said. However, once he has decided upon a biosimilar, that is the agent he sticks with for any given patient. Each biosimilar has a 4-letter suffix as part of its generic name, which does not have any meaning other than to help pharmacists and clinicians distinguish between individual agents. “We don’t just say ‘biosimilar trastuzumab’; it’s the actual name that we use,” he noted.

**INCORPORATING BIOSIMILARS INTO CLINICAL PRACTICE**

When patents expire, multiple biosimilars for the reference biologic are typically developed. For example, approximately 9 filgrastim biosimilars are available in Europe and 2 in the United States. As biosimilars are not exactly the same as their reference counterparts, the panelists explored how clinicians decide which one to choose.

Kashyap Patel, MD, said the decision is based on multiple

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**FIGURE.** Process for Approving Biologics Versus Biosimilars

For biosimilars, the most extensive work involves assessing the structure of the product and ensuring its purity. Thereafter, the product is assessed in vivo, usually in animal models, to make sure its activity and functional attributes are like the originator. Human studies are then conducted, including pharmacokinetic (PK) and pharmacodynamic (PD) studies to show that the body handles the biosimilar in a similar manner to the reference biologic. Finally, a large-scale trial is conducted to demonstrate that the biosimilar’s safety and efficacy are equivalent to the reference biologic.
BIOSIMILARS

Although this may not seem to be a big deal, he said. Two other important factors concern cost, including patient assistance programs, which may be especially important for patients who do not have adequate insurance coverage, and payer coverage, which can vary greatly between managed care organizations, including Medicare Advantage Plans.

Although biosimilars are less expensive than their reference biologics, they do not provide the same cost savings as generic drugs, which has resulted in some skepticism regarding their use. Patel explained why the 2 are vastly different. "A generic drug is a small molecule, which probably has about 180 to 300 dalton atomic weight. When we look at the biosimilar, it’s about 180,000 dalton atomic weight. It’s much more complicated. And the manufacturer must spend hundreds of millions of dollars [on rigorous evaluation]. It’s not like buying a 1-kg molecule for $1 million and then cutting pills and filling bottles,” Patel said.

Nevertheless, he said these agents are still enabling significant cost savings. At his clinic in the South Carolina tobacco belt, where he sees many patients with metastatic NSCLC, use of a bevacizumab (Avastin) biosimilar is projected to result in significant cost reductions. “By December 2021, my total drug spending will go down by about 15% to 17%. And it’s based on the fact that the history of biosimilars has shown in the last 2 years, that within 2 years, the ASP [average sales price] drops by about 30% to 35%. Fifty percent of my total drug budget is in biologics. So, when I extrapolate 35% savings in biologics, my total drug budget would go down by 15%, which is almost $1 million-plus savings to us,” he said.

But the cost savings does not just extend to clinics, he noted. Patel said that this also translates to cost reductions for patients. “Even a 30% reduction in out-of-pocket cost could save them $100 a month,” he said. Although this may not seem to be a big savings, it can be significant, especially for those who depend on Medicare or Medicaid.

However, there have been challenges getting payers onboard with biosimilars, despite the cost savings. Patel said he had to write a letter to his state’s Medicaid making a case for their use. To his surprise, his appeal worked, and the agency started approving them. He also met several times with the chief medical officers of his state’s commercial insurances, explaining that they may ultimately be able to save billions of dollars by providing coverage for biosimilars, which was nevertheless met with reluctance.

“There are so many middlemen between them,” Patel said, noting that these middlemen often advise commercial insurers that the use of biologics will provide greater discounts at the back end, such as through rebates. He emphasized the importance of educating all players, including payers and physicians, regarding the benefits of biosimilars. “I think in my experience, it [comes down to] the education of the payers, when you look at the payer battle, as well as the education of physicians concerning the approval of biosimilars. Europe has been using biosimilars since 2006. They have used over 700 million unique doses and still have not seen any adverse outcomes,” he said.

IMPRESSING BIOLOGIC ACCESS: ION AND COA EFFORTS

Patel has worked with both the International Oncology Network (ION), a business group, and the Community Oncology Alliance (COA), a not-for-profit advocacy group, to expand access to biosimilars. He has been involved in multiple educational events at ION’s national meetings to educate physicians about biosimilars. He has also contacted payers to advocate for coverage and is currently chairing a biosimilars committee. The organization advocates for the use of biosimilars across the board, rather than for individual products, he explained.

“ION tends to be agnostic regarding the manufacturer. They want to work with all the manufacturers who are willing. And there’s going to be regional variation based on the payer coverage,” he said. According to Patel, the organization helps to steer the contracting and then lets individual practices decide how they want to work with the suppliers. Subsequently, if 5 different biosimilars are available for a product, ION will try to contract with all 5 of them, and it will then leave it up to individual practices to determine which one(s) to use.

In contrast to ION, COA has been working to educate clinicians on the relevance of biosimilars in addressing Part B drug pricing and keeping pricing as low as possible. “We want to do everything possible to reduce the drug price in conjunction with the government, Senate, Congress, and payers,” Patel concluded.

REFERENCES

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