AI Makes Inroads Into Oncology Practice

PEER EXCHANGE

GENITOURINARY MALIGNANCIES
Evaluating the New Landscape in Nonmetastatic CRPC

OnePathways

HEMATOLOGIC MALIGNANCIES
Efforts to Target CD38 in Myeloma Advance

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Oncology Trials Move Forward

CLINICAL PERSPECTIVES
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Edward B. Garon, MD, MS, Details New MET+ LUNG CANCER Option

VANDERBILT-INGRAM CANCER CENTER
Evidence Supports Value of Physical Activity in Patients With Cancer
BY REENA V. JAYANI, MD

OncLive.com
Bringing the Global Oncology Community Together
1L MAINTENANCE¹

Indicated for first-line maintenance treatment of advanced ovarian cancer after response to platinum-based chemotherapy.

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.
THE FIRST AND ONLY ONCE-DAILY ORAL PARP INHIBITOR FOR PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER¹-³

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS¹,⁴

--- VISIT ZEJULA.COM/HCP TO LEARN MORE ABOUT THE PRIMA TRIAL. ---

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 were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

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

Please see Brief Summary on the following pages.


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

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PP-ZEJUS-0953
NRPADVT2000029 May 2020
Produced in USA.
**Table 1: Recommended Dose Modifications 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>Discontinue medication. (one 150 mg capsule)</td>
<td>Discontinue medication. (one 150 mg capsule)</td>
</tr>
</tbody>
</table>

*If further dose reduction below 100 mg/day is required, discontinue ZEJULA.*

---

**Table 2: Dose Modifications for Non-hematologic Adverse Reactions**

- **CTCAE Grade 3 or 4 adverse reactions:**
  - Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction.
  - Resume ZEJULA at a reduced dose per Table.

- **CTCAE Grade 5 adverse reactions:**
  - Discontinue ZEJULA.

**Table 3: Dose Modifications for Hematologic Adverse Reactions**

- **Neutrophil count <0.5 x 10^9/L or lymphocyte count <0.5 x 10^9/L:**
  - Withhold ZEJULA for a maximum of 28 days and monitor counts weekly until counts return to ≥1.0 x 10^9/L.
  - Resume ZEJULA at a reduced dose per Table.
  - Discontinue ZEJULA if neutrophil count and/or lymphocyte count remain below 0.5 x 10^9/L for 2 or more cycles.

**Table 4: Adverse Drug Reactions Reported in ≥1% of All Patients Receiving ZEJULA in PRIMA**

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA</td>
<td>Placebo</td>
</tr>
<tr>
<td>ZEJULA</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Cardiovascular Effects**

Hypertension and hyperensive 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 recipients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

- In QINQOA, Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients compared to 2% of placebo recipients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 13 days (range: 1 to 61 days). Discontinuation due to hypertension occurred in 1% of patients.

- In QINQOA, 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% of patients.

**Adverse Events**

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

- **Medullary Suppression/Meiosis Myeloid Leukemia**
- **Bone Marrow Suppression**
- **Cardiovascular Effects**
- **Clinical Risk Experience**
- **Possible Effects**
- **Possible Myelodysplastic syndrome or acute myeloid leukemia (MDS/AML)**
- **Dosing Forms and Strengths**
- **CONTRAINDICATIONS**
- **WARNINGS AND PRECAUTIONS**
- **Myeloid Dysplastic Syndrome/Myeloid Leukemia**
- **Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)**
- **Nausea**
- **Neutropenia**
- **Renal Impairment**
- **Renal Failure**
- **Stomatitis**
- **Stomatitis**
- **Stomatitis**
- **Stomatitis**

---

**Table 5:** The table summarizes the common adverse reactions and dose modifications for patients treated with ZEJULA in the PRIMA study.
Table 4. Adverse Drug Reactions Reported in ≤25% of All Patients Receiving ZELEA in PRIMA (continued)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELEA N=464</td>
<td>Placebo N=244</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>Investigations</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>12</td>
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</tr>
<tr>
<td>Osteonecrosis</td>
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<td>3</td>
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<td>Dyspnea</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 5. Abnormal Laboratory Findings in ≤25% of All Patients Receiving ZELEA in PRIMA

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELEA N=464</td>
<td>Placebo N=244</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
<td>66</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74</td>
<td>63</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased platelets</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased lymphocytes</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>66</td>
<td>63</td>
</tr>
</tbody>
</table>

Note: 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 ZELEA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELEA N=169</td>
<td>Placebo N=86</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>70</td>
<td>63</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>63</td>
<td>55</td>
</tr>
</tbody>
</table>

Note: 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.

Maintenance Treatment of Recurrent Ovarian Cancer
The safety of ZELEA monotherapy 200 mg once daily has been studied in 167 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 45% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZELEA in these patients was 2.96 days.

Table 8. Adverse Drug Reactions Reported in ≤25% of All Patients Receiving ZELEA in NOVA

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELEA N=198</td>
<td>Placebo N=149</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Increased anemia</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Note: 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 9. Normal Laboratory Findings in ≤25% of All Patients Receiving ZELEA in NOVA

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELEA N=198</td>
<td>Placebo N=149</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Increased anemia</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Note: 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.

Cardiac Disorders
Palpitations                                       | 10 | 2 | 0 | 0 |

Gastrointestinal Disorders
Nausea                                             | 12 | 3 | 1 | 0 |

Vascular Disorders
Hypertension                                       | 12 | 3 | 1 | 0 |

General Disorders and Administration Site Conditions | 12 | 3 | 1 | 0 |

Fatigue                                           | 12 | 3 | 1 | 0 |

Metabolism and Nutrition Disorders                  | 12 | 3 | 1 | 0 |

Increased appetite                                  | 12 | 3 | 1 | 0 |

Increased anemia                                    | 12 | 3 | 1 | 0 |

Increased thrombocytopenia                           | 12 | 3 | 1 | 0 |

Increased platelets                                  | 12 | 3 | 1 | 0 |

Increased leukocytes                                 | 12 | 3 | 1 | 0 |

Increased alkaline phosphatase                      | 12 | 3 | 1 | 0 |

Increased creatinine                                 | 12 | 3 | 1 | 0 |

Increased magnesium                                  | 12 | 3 | 1 | 0 |

Increased aspartate aminotransferase                 | 12 | 3 | 1 | 0 |

Increased alanine aminotransferase                   | 12 | 3 | 1 | 0 |

Patients Receiving ZELEA with Dose Based on Baseline Weight or Platelet Count in PRIMA

Among patients who received ZELEA with the dose based on weight and platelet count, the median duration of treatment was 11.9 months (range 1 day to 16 months). Serious adverse reactions occurred in 7% of patients receiving ZELEA. Serious adverse reactions in >2% of patients were anemia (8%), and thrombocytopenia (3%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZELEA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZELEA included thrombocytopenia and anemia (10% each), and nausea (2%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (25%), and neutropenia (15%).

Table 6. Adverse Drug Reactions Reported in ≤25% of All Patients Receiving ZELEA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grades 1–4</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZELEA N=169</td>
<td>Placebo N=86</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>
**Table 4: Adverse Reactions Reported in ≥10% of Patients Receiving ZELURON in NOV (continued)**

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

**CTCAE—Common Terminology Criteria for Adverse Events version 4.02**

Includes preferred terms of neopterin infection, neopterin neopterin, and neopterin neopterin.

<table>
<thead>
<tr>
<th>Table 5: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELURON in NOV</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURON N=367</td>
<td>Placebo N=207</td>
<td>ZELURON N=367</td>
</tr>
<tr>
<td><strong>Decrease in hemoglobin</strong></td>
<td>85</td>
<td>56</td>
</tr>
<tr>
<td><strong>Decrease in platelet count</strong></td>
<td>72</td>
<td>21</td>
</tr>
<tr>
<td><strong>Decrease in WBC count</strong></td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td><strong>Decrease in absolute neutrophil count</strong></td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td><strong>Increase in AST</strong></td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td><strong>Increase in ALT</strong></td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 6: Adverse Reactions Reported in ≥15% of Patients Receiving ZELURON in QI UDA (continued)**

**Investigations**

| Blood alkaline phosphatase increased | 11 | 2 |
| AST/ALT elevated | 11 | 1 |

**Metabolism and Nutrition Disorders**

| Decreased appetite | 27 | 2 |

**Musculoskeletal and Connective Tissue Disorders**

| Musculoskeletal pain | 29 | 3 |

**Nervous System Disorders**

| Headache | 19 | 0.4 |
| Business | 13 | 0 |

**Psychiatric Disorders**

| Insomnia | 21 | 1 |
| Renal and Urinary Disorders | 17 | 1 |

**Respiratory, Thoracic and Mediastinal Disorders**

| Dyspnea | 22 | 3 |
| Cough | 13 | 0 |

**Vascular Disorders**

| Hemorrhage | 14 | 5 |

**Table 7: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELURON in QI UDA**

<table>
<thead>
<tr>
<th>ZELURON N=367</th>
<th>Placebo N=207</th>
<th>ZELURON N=367</th>
<th>Placebo N=179</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Increased lymphocytes</td>
<td>57</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Decreased nephrops</td>
<td>34</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Table 8: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELURON in QI UDA**

<table>
<thead>
<tr>
<th>ZELURON N=367</th>
<th>Placebo N=207</th>
<th>ZELURON N=367</th>
<th>Placebo N=179</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Increased lymphocytes</td>
<td>57</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40</td>
<td>8</td>
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<tr>
<td>Increased creatinine</td>
<td>36</td>
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</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Table 9: Adverse Reactions Reported in ≥15% of Patients Receiving ZELURON in QI UDA**

**Blood and Lymphatic System Disorders**

| Anemia | 51 | 27 |
| Thrombocytopenia | 52 | 28 |
| Neutropenia | 20 | 13 |

**Gastrointestinal Disorders**

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

**General Disorders and Administration Site Conditions**

| Fatigue | 56 | 7 |
| Infections and Infestations | 15 | 2 |

**Postmarketing Experience**

**The following adverse reactions have been identified during post-approval use of ZELURON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Immunologic System Disorders: hypersensitivity (including anaphylaxis).**

**Neurologic System Disorders:** primary reproductively competent syndrome (PPCS)

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

**Respiratory, Thoracic, and Mediastinal Disorders:** reproductively potential carcinogens

**Skin and Subcutaneous Tissue Disorders:** psoriasis

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, ZELURON can cause fetal harm when administered to pregnant women. There are no data regarding the use of ZELURON in pregnant women to inform the drug-associated risk. The potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with ZELURON. Because animal reproduction studies are not always predictive of human response, additional risk cannot be ruled out. Additionally, women are at high risk of increasing risk of spontaneous abortion and fetal death. Increased risk of spontaneous abortion and fetal death is increased if the drug is administered during pregnancy.

**Lactation**

| Risk Summary | No data available regarding the presence of neopterin in breast milk. Lowering its effect on the breast-fed infant or milk production. Because of the potential for serious adverse reactions in breast-fed infants receiving ZELURON, a nursing woman not to breastfeed during treatment with ZELURON and for 6 months after the last dose.

**Females and Males of Reproductive Potential**

Procedures for women:

ZELURON can cause fetal harm when administered to a pregnant woman. See Use in Specific Populations in the drug information for ZELURON.

**Procedures for men:**

Male use in ZELURON is not recommended due to use effective contraception during treatment with ZELURON and for at least 6 months following the last dose.

**Idiopathic**

Males:

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

**Pediatric Use**

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

**Geriatric Use**

In PRM, 21% of patients aged >65 years and 4% were ≥75 years. In NOV, 33% of patients were aged >65 years and 8% were ≥75 years. NOV, 33% of patients were aged >65 years and 8% were ≥75 years. NOV, 8% of patients were aged >65 years and 8% were ≥75 years. NOV, 8% of patients were aged >65 years and 8% were ≥75 years.

**Renal Impairment**

No adjustment is necessary for patients with mild (CLcr 60 to 85 mL/min) or moderate (CLcr 30 to 50 mL/min) renal impairment. The dose of renal impairment was determined by renal function as estimated by the Cockcroft-Gault equation. The safety of ZELURON in patients with moderate to severe renal impairment is not known.

**Drug Interactions**

No dose adjustment is recommended in patients with mild to moderate hepatic impairment according to the National Cancer Institute's Drug Interactions Working Group. The safety of ZELURON in patients with moderate to severe hepatic impairment is not known.

**OVERDOSAGE**

There is no specific treatment in the event of ZELURON 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**

**Patient Information:**

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

**Morbidity:**

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding, nausea, headaches, tremors in bone or muscle, and other laboratory findings of blood cell counts, or a need for transfusions. This may be a sign of hematologic toxicity or reproductively potential (PPCS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZELURON (see Warnings and Precautions).

**Other Morbidity:**

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

**Cardiovascular Effects:**

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first 4 months, and monthly for the first year of treatment, and then periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated (see Warnings and Precautions).

**Dosage and Administration:**

Inform patients on how to take ZELURON (see Dosage and Administration). ZELURON should be taken once daily for patients without a history of drug allergy or who are taking ZELURON immediately after the last dose (see Use in Specific Populations).

**Contraindications:**

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

**Lactation:**

Advise females not to breastfeed while taking ZELURON and for 1 month after the last dose (see Use in Specific Populations).

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**PP-ZEUUS-0986**

**NRPBFL2500003 May 2020**

**Produced in USA.**

**Manufacturer:** GlaxoSmithKline

**Research Triangle Park, NC 27709**

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AI Makes Inroads Into Oncology Practice

by DENISE MYSHKO

Treatment algorithms that leverage artificial intelligence (AI) to help identify patients with cancer who are at risk of relapse or serious adverse effects are gaining ground in the oncology field. Although these analytical tools have not made a significant impact on daily practice yet, experts say they probably will within the next several years. Clinical observers discuss how this trend is shaping up.

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New Steps Are Needed to Manage Data Overload

DURING THE MONTH OF MAY, the FDA approved 7 new drugs, combinations, or indications for patients with non–small cell lung cancer.¹ That explosion of activity represents a staggering amount of data for thoracic oncology specialists to evaluate, particularly because these new options come amid a decade of extraordinary innovation in this field. The latest approvals are for molecularly targeted regimens and immunotherapies—2 areas that have blossomed just in the past 5 years.

Beyond lung cancer, the bounty of novel therapies has become a welcome but challenging predicament. Although it is invigorating to have new therapeutic strategies, busy practitioners must find time to absorb an array of clinical findings and relate these data specifically to the patients they treat in their clinics.

The theme of how best to navigate the continuing barrage of new clinical information emerges in this issue of OncologyLive® in several ways. In our cover story, “AI Makes Inroads Into Oncology Practice,” we delve into the artificial intelligence (AI) decision support tools that are starting to make their way to the front lines of cancer care.

Certainly, we’ve been hearing about the promise of systems that leverage “big data” for years. Now, companies such as COTA, a health care technology provider that analyzes real-world data, and cancer centers are developing useful tools for clinical practice. Such systems can help predict, for example, the likelihood that an individual patient will wind up seeking emergency department care. One particularly challenging technological hurdle has been integrating the thousands of bits of information in an electronic health record into an algorithm that correlates these data points with best practices and guidelines. Emerging AI approaches are addressing these concerns.

In another aspect of the information dilemma, our editor-in-chief, Maurie Markman, MD, discusses the difficulties of trying to choose the best course of treatment when new drug approvals and indications have resulted in multiple therapeutic options for similar patient populations without comparative data. Markman argues in his column that the oncology research community must find a way to directly compare drugs and strategies to answer clinically meaningful questions, even if finding the funding for such studies would be difficult.

These thoughts on how best to move the oncology field forward are important to ponder for those most involved in seeking to determine patient care.

As always, thank you for reading—and stay safe.

Mike Hennessy Sr
Chairman and Founder

REFERENCES

Here are many lessons to be learned from the rapidly evolving coronavirus disease 2019 (COVID-19) pandemic. These include the need for objectively valid scientific expertise and knowledge in guiding public health policy to optimize the chances that individuals will remain safe while ensuring that our society effectively deals with the immediate consequences of the pandemic and develops essential plans for the future.

Two aspects of clinical research into COVID-19 are particularly striking and may offer lessons for the oncology field. First, the impressively large number of individuals who have quickly agreed to participate as research subjects in COVID-19 treatment and vaccine trials emphasizes the general willingness of members of our society to join in efforts to help develop scientifically rigorous knowledge that will critically inform efforts to cure or prevent this terrible infectious illness.1 This observation supports surveys conducted over the years regarding the considerable interest among patients with cancer in participating in clinical research studies that not only may improve their own condition but also generate information that will be beneficial for future generations of individuals with a malignancy. Such data are highly relevant for the potential acceleration of efforts to discover clinically meaningful advances in cancer management through the conduct of scientifically rigorous investigation.

However, another facet of COVID-19 research is not such a positive development. That is the potential that well-intentioned but unfortunately poorly focused and uncoordinated clinical research efforts will not be in the public’s best interest. As noted in a recent commentary in Science, there are more than 18 ongoing clinical trials that plan to enroll 75,000 patients in North America examining a variety of hydroxychloroquine regimens for the treatment of COVID-19.2 Is this number of trials and research subject requirements necessary or—far more importantly—helpful? How many of these studies are essentially identical in their scientific goals, patient populations, and study end points? How many of these studies are optimally designed such that they have the potential to reach a scientifically valid and clinically meaningful end point versus those that may yield misleading results by being underpowered or by having some other serious protocol design flaw?

The explosion of COVID-19 studies illustrates questions that have plagued oncology research. To be clear, these concerns are not meant to suggest that studies designed for initial or subsequent drug regulatory approvals in the oncology arena suffer from inadequate design or inappropriate conclusions. Rather, the focus here is on the impact of multiple clinical research efforts undertaken by individual pharmaceutical/biotech companies in the development of their products.

Unanswered Questions
Although such studies are an appropriate and understandable part of the regulatory process, when a new or established antineoplastic agent receives marketing approval as a single agent or in a combination regimen, oncologists are forced to quickly—and essentially on their own—examine the merits of the new offering within the context of existing or other recently approved products in the absence of clinically meaningful comparative data.

Consider, for example, the nearly simultaneous approval of 2 PARP inhibitor agents for the management of previously treated prostate cancer. The drugs differ in on-label requirements for prior therapy and, perhaps most relevant, in mandated biomarkers for selecting the patient population most likely to achieve clinical benefit. Of course, the reason for this state of affairs is the simple fact that the individual studies that resulted in regulatory approval for the drugs differed somewhat in their eligibility and ineligibility criteria as well as in other clinically relevant factors. So in the absence of comparative data for the 2 agents, the treating oncologist is left to decide which strategy is optimal for their patients.
Perhaps in no area of oncology is this confusing status quo of greater concern than in ovarian cancer. There are currently 3 PARP inhibitors approved as second-line or later maintenance therapy for patients with this malignancy who have achieved a complete or partial response to platinum-based chemotherapy.\(^3,4\) And, from a regulatory perspective in the United States, biomarker evidence of a BRCA mutation or other evidence of DNA repair deficiency is not required for use of these agents in the second-line or later setting. Additionally, the antiangiogenic agent bevacizumab (Avastin) is approved in essentially the same clinical setting in combination with a platinum drug and as single-agent maintenance therapy.\(^3\) Thus, practicing oncologists have at least 4 therapeutic approaches in this setting that they and their patients must consider in the absence of randomized comparative data to assist in this decision-making process.

Added to this mix of independent highly positive clinical trial data that may confuse rather than inform management decisions are the results from several first-line ovarian cancer studies that examined 2 different PARP inhibitors and in 1 case, the use of a PARP inhibitor combined with bevacizumab.\(^5,7\) Again, regulatory approval was appropriately based on the individual trial designs and strategies that included different approaches to patient selection, duration of maintenance drug administration, and biomarkers.

One solution to this clinical dilemma might be to directly compare the drugs and approaches that may be reasonably employed in ovarian cancer (eg, single-agent vs combination regimens, duration of therapy, specific molecular biomarker platforms, etc) in several pragmatic clinical trials specifically designed to address the question most relevant to the patient. That question is most likely to be: “Of the currently available agents and delivery strategies that might be considered in my situation, what is best for me?”

Considering the importance of this question, trial accruals likely would not be an issue, and multiple clinically meaningful questions could certainly be answerable over a relatively short period of time. Although there are many complex issues associated with such a suggestion—including the essential issue of study funding—perhaps it is finally time to give this concept a try.

**REFERENCES**

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 60.
FDA DIGEST

Frontline HCC Paradigm Now Includes Combination Atezolizumab and Bevacizumab

The approval of atezolizumab (Tecentriq) in combination with bevacizumab (Avastin) for patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy expands the limited stock of frontline treatment options for patients with this disease.

The doublet therapy’s indication in this setting is based on findings from the phase 3 IMBrave150 study (NCT03434379), which demonstrated a 42% decrease in the risk of death with the regimen compared with standard-of-care sorafenib (Nexavar; HR, 0.58; 95% CI, 0.42-0.79; P = .0006). The combination was also associated with a 41% reduction in the risk of disease progression or death versus sorafenib (HR, 0.59; 95% CI, 0.47-0.76; P<.0001).

TO READ MORE, VISIT www.onclive.com/link/8155.

Advanced GIST Paradigm Gains Ripretinib

Ripretinib (Qinlock) can now be administered to adults with gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib (Gleevec).

The agent’s approval is based on findings from the phase 3 INVICTUS trial (NCT03353753), in which the investigational broad-spectrum KIT and PDGFRa inhibitor reduced the risk of disease progression or death by 85% in patients with heavily pretreated, advanced disease. The median progression-free survival was 6.0 months with ripretinib compared with 1.0 months with placebo (HR, 0.15; 95% CI, 0.09-0.25; P<.0001). The survival advantage extended to all patient subgroups, investigators said.

The median overall survival was also longer with ripretinib (15.1 vs 6.6 months; HR, 0.36; 95% CI, 0.20-0.63; P = .0004), and at 12 months, continued to favor the switch kinase inhibitor. The 12-month overall survival rates were 65.4% (95% CI, 51.6%-76.1%) and 25.9% (95% CI, 7.2%-49.9%) with ripretinib and placebo, respectively.

TO READ MORE, VISIT www.onclive.com/link/8060.

First Therapy Is Approved for Kaposisarcoma in More Than 20 Years

The historically limited tool kit of treatment options for Kaposisarcoma broadens with the approval of pomalidomide (Pomalyst), which is now indicated for patients with AIDS-related Kaposisarcoma whose disease has become resistant to highly active antiretroviral therapy or HIV-negative disease.

The agent’s accelerated approval is based on data from the single-arm phase 1/2 12-C-0047 study (NCT01495598), which showed that pomalidomide induced an overall response rate of 71% (95% CI, 51%-87%) in patients with HIV-positive (n = 18) and HIV-negative (n = 10) symptomatic Kaposisarcoma. This finding included a 14% complete response rate and a 57% partial response rate. The median duration of response was 12.1 months and 10 of the 20 patients who responded remained in response for 12 months or longer.

Pomalidomide has a different mechanism of action from the cytotoxic chemotherapy agents that are typically used to treat this rare disease, which occurs at a rate of about 6 cases per million people each year in the United States.

Of note, pomalidomide is only available through the FDA Risk Evaluation and Mitigation Strategy program.

TO READ MORE, VISIT www.onclive.com/link/8034.

A Series of Frontline Approvals Advances the NSCLC Paradigm

The latest wave of FDA approvals for patients with non–small cell lung cancer (NSCLC) adds new frontline options to the treatment paradigm. The most recent first-line approvals include the combination of ramucirumab (Cyramza) plus erlotinib (Tarceva), nivolumab (Opdivo) plus ipilimumab (Yervoy), and single-agent atezolizumab (Tecentriq).

Ramucirumab and Erlotinib for EGFR+ Disease

The approval of ramucirumab in combination with erlotinib for adults with metastatic disease that harbors either EGFR exon 19 deletions or exon 21 (L858R) substitution mutations brings a new targeted option to NSCLC frontline treatment.

The doublet therapy demonstrated its efficacy in the phase 3 RELAY study (NCT02411448), in which the addition of ramucirumab to erlotinib led to a 41% reduction in the risk of disease progression or death compared with erlotinib alone. At a median follow-up of 20.7 months, the investigator-assessed median progression-free survival (PFS) was 19.4 months (95% CI, 15.4-21.6) with the combination versus 12.4 months (95% CI, 11.0-13.5) with erlotinib monotherapy (HR, 0.59; 95% CI, 0.46-0.76; P<.0001).

The PFS benefit was observed across genomic subgroups: in patients with exon 19 deletions, the median PFS was 19.6 months and 12.5 months with the doublet therapy and the single-agent, respectively (HR, 0.651; 95% CI, 0.469-0.903). Among those with exon 21 substitutions, the median PFS was 19.4 months with ramucirumab plus erlotinib compared with 11.2 months with erlotinib.

TO READ MORE, VISIT www.onclive.com/link/8175.

Frontline Nivolumab and Ipilimumab

Frontline treatment options for patients with metastatic or recurrent NSCLC that does not harbor EGFR or ALK genomic tumor aberrations now include nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.

The approval is based on findings from the phase 3 CheckMate-9LA trial (NCT03215706), which demonstrated a superior overall survival benefit with the regimen compared with up to 4 cycles of chemotherapy alone followed by optional maintenance treatment in patients with advanced disease (14.1 vs 10.7 months; HR, 0.69; 95% CI, 0.55-0.87; P = .0006). The median PFS was 6.8 months in the nivolumab-ipilimumab arm and 5.0 months in the platinum-doublet chemotherapy arm (HR, 0.70; 95% CI, 0.57-0.86; P = .0001). Additionally, the overall response rate was 38% and 25%, respectively.

Earlier in May, the FDA approved the combination of nivolumab plus ipilimumab as first-line therapy for patients with PD-L1 expression of 1% or greater.

TO READ MORE, VISIT www.onclive.com/link/8133.

Atezolizumab for PD-L1–Positive Disease

Atezolizumab is now indicated for the first-line treatment of adults with high PD-L1–expressing metastatic NSCLC without EGFR or ALK genomic tumor aberrations. High PD-L1 expression, which must be determined by an FDA-approved test, is defined as PD-L1 that stains 50% or more of tumor cells or PD-L1–stained tumor-infiltrating immune cells covering 10% or more of the tumor area.

The immune checkpoint inhibitor’s approval is based on findings from the phase 3 IMpower110 trial (NCT02409342), which showed that atezolizumab monotherapy led to a 7.1-month improvement in overall survival versus chemotherapy in this patient population (20.2 vs 13.1 months; HR, 0.59; 95% CI, 0.40-0.89; P = .0106).

TO READ MORE, VISIT www.onclive.com/link/8078.
**Drug Spotlight | NIRAPARIB (ZEJULA)**

**Niraparib’s Indication Expands in Ovarian Cancer**

by RACHEL NAROZNIK, MA

**NIRAPARIB (ZEJULA),** a PARP inhibitor that has shown efficacy across various subtypes of ovarian cancer with a manageable safety profile, finds further utility in a broader population of patients with this disease.

On April 29, 2020, the FDA approved niraparib as a maintenance therapy for adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with a complete or partial response to first-line platinum-based chemotherapy.

Niraparib’s latest approval is based on progression-free survival (PFS) data from the phase 3 PRIMA study (NCT02655016), which demonstrated a statistically significant improvement in both PRIMA’s homologous recombination deficiency (HRD) subset and overall population. The median PFS among patients with HRD was 21.9 months with niraparib compared with 10.4 months with placebo (HR, 0.43; 95% CI, 0.31-0.59; P <.0001). In the overall population, the median PFS was 13.8 months in the niraparib arm and 8.2 months in the placebo arm (HR, 0.62; 95% CI, 0.50-0.76; P <.0001).

In an interview with OncologyLive®, Bhavana Pothuri, MD, a lead author on the PRIMA study and a professor in the Department of Obstetrics and Gynecology at New York University Grossman School of Medicine, and a gynecologic oncologist at New York University Langone Perlmutter Cancer Center, both in New York, discusses the practice-changing implications of niraparib’s approval.

**Please provide an overview of the patient population.**

The PRIMA study enrolled 733 women with advanced high-grade ovarian cancer or endometrial ovarian cancer who were randomized to receive either niraparib or placebo, and then stratified based on whether or not they had received neoadjuvant chemotherapy, whether their response to chemotherapy was a complete or a partial response, and finally, whether there was homologous recombination deficiency.

Patients initially received a fixed dose of niraparib at 300 mg once a day, but about two-thirds of the way through this study, this [regimen] was amended to give patients an individualized dose of either 200 mg or 300 mg based on their baseline body weight and platelet count.

PRIMA included patients who had high risk of relapse: 35% of patients had stage IV disease. About 5% of patients had HRD tumors.

**What was notable about the survival data that led to the approval?**

PRIMA used a hierarchical analysis of progression-free survival. The HRD population was evaluated first, and the median progression-free survival was significantly increased in patients receiving niraparib versus placebo. These data were really impressive, [so] the next step was to look at the overall population. Niraparib significantly improved progression-free survival in both the HRD and the overall population. This is why the FDA approval of niraparib is for the entire PRIMA population.

**What is niraparib’s mechanism of action?**

Niraparib is a PARP inhibitor, [which is] of interest in ovarian cancer due to the loss of the DNA repair machinery in high-grade serous epithelial ovarian cancer and high-grade endometrial ovarian cancer. [This allows us] to exploit this deficiency for a therapeutic advantage, [which] is known as synthetic lethality. There are 2 main pathways that are important for this repair of double-stranded DNA breaks, either through homologous recombination or nonhomologous and rejoining pathways.

**Please describe niraparib’s safety profile.**

The safety data that we saw in this trial was consistent with what was reported previously in the ENGOT-OV16/J NOVA trial, [NCT01847274; where] the most common adverse events were anemia, nausea, and thrombocytopenia.

Thrombocytopenia has been one of the problematic toxicities with this drug. We prospectively evaluated data from the PRIMA trial and adjusted [them] for [patients who weighed] less than 77 kg or had a platelet count of less than 150,000. When we began individualized dosing, the blinded, pooled safety data noted that the incidence of grade 3 or higher hematologic and nonhematologic toxicities decreased.

There was [also] a greater than 60% reduction in grade 3 or grade 4 thrombocytopenia, and grade 4 thrombocytopenia and platelet transfusions decreased by 80%.

We conducted quality-of-life analyses to see if these higher-risk hematologic toxicities impacted overall health-related quality of life. The preliminary data that have been presented so far seem to suggest that there is no [effect].

**How does niraparib’s mechanism of action expand the ovarian cancer paradigm?**

Niraparib establishes a new standard of care for women with platinum-sensitive recurrence who have had a response to platinum-based chemotherapy. Prior to this study, only patients with BRCA1 or BRCA2 mutations [received] a PARP inhibitor in the frontline setting, so the ability to move a PARP inhibitor into the up-front setting is incredible.

Niraparib is currently listed as a maintenance option following frontline therapy in the NCCN [National Comprehensive Cancer Network] guidelines for ovarian cancer. This approval is a huge win for our patients with ovarian cancer because niraparib is approved for use regardless of BRCA status, HRD, or histology, and does not require a companion diagnostic.

**What are the next steps for this agent?**

Studies are currently ongoing with combinations of niraparib [including] checkpoint inhibitors, antiangiogenesis agents, and other targeted therapies. It will be important to see if we can further improve upon these results.

[Many] trials have been performed in patients who had never received a PARP inhibitor, so the challenge is [determining] what we do for patients who have already been treated with a PARP inhibitor during frontline maintenance therapy. Will PARP inhibitors have activity after upfront therapy in certain patients? Further studies are going to help elucidate some of these questions.

**How does this approval expand niraparib’s utility in ovarian cancer?**

As stated above, the approval is for all-comers who have had a response to initial platinum-based chemotherapy in the frontline setting. We have been talking about maintenance therapy, [but] niraparib was also approved in October of 2019 [based on results from] the phase 2 QUADRA trial [NCT02354586]. Niraparib’s approval for platinum-sensitive patients with recurrent ovarian cancer and HRD was due to the response rate that was seen in this study.

Niraparib is the first PARP inhibitor to be approved beyond just BRCA1 and [BRCA2] [and] expands therapy for treatment beyond the biomarker-positive population to patients [with HRD, who] account for about 50% of our ovarian cancers.
FDA new indication approval—April 29, 2020
FDA grants approval for the PARP inhibitor niraparib (Zejula) for the maintenance treatment of adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with a complete or partial response to first-line platinum-based chemotherapy.

Mechanism of action:
• Niraparib inhibits the PARP-1 and PARP-2 enzymes, which aid DNA repair.
• In vitro studies have shown that niraparib-induced cytotoxicity, which has been observed in tumor cell lines with or without BRCA 1/2 deficiencies, may lead to increased formation of PARP-DNA complexes, resulting in DNA damage, apoptosis, and cell death.
• Niraparib decreased tumor growth in human-derived xenograft tumor models with homologous recombination deficiency (HRD) and either mutated or wild type BRCA 1/2.

How supplied:
• 100-mg capsules

Dosing:
• Patients weighing less than 170 lbs or with a platelet count of less than 150,000/μL: 200 mg once daily
• Patients weighing 170 lbs or more and with a platelet count of 150,000/μL or higher: 300 mg once daily

Company: GlaxoSmithKline

PIVOTAL EFFICACY DATA FOR APPROVAL
PRIMA (NCT02655016) is a placebo-controlled trial that enrolled 733 patients with advanced ovarian cancer with complete or partial response to first-line platinum-based chemotherapy. Patients with HRD tumors were permitted to participate. HRD status, which was defined as BRCA-mutant tumors or a genomic instability score of 42 or greater, was determined using the Myriad myChoice CDx assay.

Efficacy results for approval in the PRIMA trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HRD population</th>
<th>Overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Niraparib (n = 487)</td>
<td>Placebo (n = 246)</td>
</tr>
<tr>
<td></td>
<td>Niraparib (n = 247)</td>
<td>Placebo (n = 126)</td>
</tr>
<tr>
<td>PFS events (%)</td>
<td>33%</td>
<td>48%</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>21.9 (19.3-NE)</td>
<td>13.8 (11.5-14.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.43 (0.31-0.59)</td>
<td>0.62 (0.50-0.76)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

HRD, homologous recombination deficiency; NE, not estimable; PFS, progression-free survival.

Warnings and precautions
• Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML): MDS/AML has been reported in patients receiving niraparib and can be fatal. Monitor patients for hematological toxicity. Discontinue treatment if MDS/AML is confirmed.
• Bone marrow suppression: Test complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter for clinically significant changes.
• Cardiovascular effects: Monitor blood pressure and heart rate weekly for the first 2 months, then monthly for the first year, and periodically thereafter. Administer antihypertensive medication or adjust dose as necessary.
• Embryo-fetal toxicity: Niraparib can cause fetal harm. Warn women of reproductive potential of the possible risk to a fetus and recommend use of effective contraception.

Commonly reported adverse events in the PRIMA study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Niraparib (n = 484)</th>
<th>Placebo (n = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66%</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>64%</td>
<td>18%</td>
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<tr>
<td>Nausea</td>
<td>57%</td>
<td>28%</td>
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<tr>
<td>Fatigue</td>
<td>51%</td>
<td>41%</td>
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<tr>
<td>Neutropenia</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>Constipation</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>Low grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39%</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
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<td>18%</td>
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<tr>
<td>Nausea</td>
<td>1%</td>
<td>2%</td>
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<tr>
<td>Fatigue</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
<td>20%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1%</td>
<td>38%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>0.4%</td>
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<tr>
<td>Insomnia</td>
<td>1%</td>
<td>15%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>12%</td>
</tr>
</tbody>
</table>

References
Drug Spotlight | DARATUMUMAB AND HYALURONIDASE-FIJH
(DARZALEX FASPRO)

Subcutaneous Daratumumab Offers Convenience for Patients With Multiple Myeloma

by DENISE MYSHKO

NEARLY 5 YEARS after its approval for patients with multiple myeloma, daratumumab (Darzalex) is now available in a formulation that can be administered in a fraction of the time required with the original agent. On May 1, 2020, the FDA approved subcutaneous daratumumab and hyaluronidase-fijh (Darzalex Faspro), which takes 3 to 5 minutes to administer instead of the hours needed for the drug’s intravenous (IV) form.1

Subcutaneous daratumumab gained indications across 5 regimens for adults in multiple myeloma settings. For patients with a new diagnosis who are ineligible for autologous stem cell transplant, the formulation can be combined with bortezomib (Velcade), melphalan, and prednisone (VMP) and in conjunction with lenalidomide (Revlimid) and dexamethasone (Rd).

In the relapsed/refractory (R/R) setting among patients who received at least 1 prior therapy, the new agent can be used with the Rd regimen or with bortezomib plus dexamethasone. As monotherapy, the drug can be administered to patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who are double refractory to those drugs.

IV daratumumab is approved in those settings, as well as in combination with bortezomib, thalidomide (Thalomid), and dexamethasone in patients with new diagnoses who are eligible for transplant and in conjunction with pomalidomide (Pomalyst) and dexamethasone in patients who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor.2

The new formulation consists of daratumumab, a monoclonal antibody directed at CD38, and human hyaluronidase, a glycosylated protein that increases the dispersion and absorption of coadministered drugs when given subcutaneously.1

Janssen Biotech, which manufactures daratumumab, collaborated with Halozyme Therapeutics, which develops the drug delivery technology. Halozyme’s Enhance system works to degrade hyaluronan, a polysaccharide found in the extracellular matrix of the subcutaneous tissue, allowing large volumes (up to 300-600 mL) to be delivered in a single subcutaneous injection.1,3 The recommended dose is 1800 mg of daratumumab with 30,000 U of hyaluronidase per 15 mL administered subcutaneously to the abdomen over 3 to 5 minutes, starting with weekly doses and then varying in frequency according to the indication.

By comparison, IV daratumumab, originally approved in 2015, has a recommended infusion rate for the first hour of treatment of 50 mL/hour during week 1 and 2 doses, increasing to 100 mL/hour for week 3 onward if there are no infusion reactions; the maximum infusion rate is 200 mL/hour. The dosing is 16 mg/kg of the patient’s body weight.2

“Subcutaneous daratumumab will be a big convenience for both patients and nurses,” Saad Z. Usmani, MD, a key investigator, said in an interview with OncologyLive®. “The days can be long for patients. It is highly likely that the subcutaneous formulation, because of the convenience factor and the low infusion reaction and similar efficacy rates, may replace the IV formulation moving forward.

“The most important thing is that the subcutaneous formulation in the 15-mL, premixed syringe can be given in under 5 minutes compared with the IV formulation, where the first IV infusion is about 7 hours, the second is 6 hours, and after that takes about 3 to 4 hours,” added Usmani, who is the division chief of plasma cell disorders and director of clinical research in hematologic malignancies at Atrium Health’s Levine Cancer Institute in Charlotte, North Carolina. He also is a clinical professor of medicine at the University of North Carolina at Chapel Hill School of Medicine.

CLINICAL AND PHARMACOKINETIC DATA

Usmani and colleagues investigated the efficacy of the subcutaneous formulation in the phase 3 COLUMBA study (NCT03277105), a noninferiority trial in which 522 patients with R/R multiple myeloma who received at least 3 prior lines of therapy were randomized to receive monotherapy with subcutaneous (1800 mg/30,000 units) or IV daratumumab (16 mg/kg). Patients in both arms were treated weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24, and once every 4 weeks starting with week 25 until unacceptable toxicity or disease progression. The primary end points were overall response rate (ORR) and the pharmacokinetic measures of maximum trough concentration levels before cycle 3.

“After follow-up of 7½ months, both of the primary end points were met for the study,” Usmani said. “The overall response was similar in both the patient populations in the subcutaneous group, the response rate was 41% and it was 37% in the intravenous group. The [trough concentration] levels for both IV and subcutaneous formulation were similar.”

Notably, there was a nearly two-thirds reduction in systemic administration-related reactions for subcutaneous daratumumab compared with IV daratumumab (13% vs 34%, respectively; OR, 0.28; 95% CI, 0.18-0.44; P < .0001).

“The common adverse events were similar in both groups except for the infusion-related reactions, which were much lower in the subcutaneous arm compared with the IV arm,” Usmani said. “That was a big improvement from a patient perspective. The majority of the infusion-related reactions were predominantly grade 1 and 2. Very few grade 3 reactions were seen.”

Additionally, the efficacy of subcutaneous daratumumab was evaluated in the multicohort phase 2 PLEIADES trial (NCT03412565). Findings from 2 cohorts of the nonrandomized study, in which patients received experimental daratumumab as part of a VMP or Rd regimen, are included on the drug’s label. In the daratumumab plus VMP group, which included 67 patients with newly diagnosed multiple myeloma ineligible for transplant, the ORR was 88% (95% CI, 78%-95%). In the daratumumab plus Rd group, with 65 patients with R/R multiple myeloma, the ORR was 91% (95% CI, 81%-97%).1

REFERENCES


FDA Approval—May 1, 2020
The FDA grants approval for daratumumab and hyaluronidase-fihj injection (Darzalex Faspro) for treatment of multiple myeloma in 5 clinical settings:
• combined with bortezomib, melphalan, and prednisone in patients with new diagnosis who are ineligible for autologous stem cell transplant;
• combined with lenalidomide and dexamethasone in patients with new diagnosis who are ineligible for transplant;
• combined with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma who have received at least 1 prior therapy;
• combined with bortezomb and dexamethasone in patients who received at least 1 prior therapy; and
• as monotherapy in patients who received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who are double refractory to those drugs.

Mechanism of action:
• Daratumumab is a monoclonal antibody that inhibits the growth of CD38-expressing tumor cells found on the surface of hematopoietic cells including multiple myeloma cells.
• Hyaluronidase, a naturally occurring enzyme, increases the permeability of the subcutaneous tissue by depolymerizing hyaluronan, a polysaccharide found in the extracellular matrix of subcutaneous tissue.

How supplied:
• Single-dose vials with 1800-mg daratumumab and 30,000 U of hyaluronidase per 15 mL

Company: Janssen Biotech

MONOTHERAPY FINDINGS FROM COLUMBA TRIAL*

<table>
<thead>
<tr>
<th></th>
<th>Subcutaneous daratumumab (N = 263)</th>
<th>Intravenous daratumumab (N = 259)</th>
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<tr>
<td>ORR (95% CI)</td>
<td>41% (35%-47%)</td>
<td>37% (31%-43%)</td>
</tr>
<tr>
<td>Relative risk (subcutaneous over IV)</td>
<td>1.11 (0.89-1.37)</td>
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</tr>
<tr>
<td>CR or better</td>
<td>1.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>VGPR</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>PR</td>
<td>22%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Intention-to-treat population.

EFFICACY FINDINGS FOR COMBINATION COHORTS IN PLEIADES TRIAL*

<table>
<thead>
<tr>
<th></th>
<th>Subcutaneous D with VMP (N = 67)</th>
<th>Subcutaneous D with Rd (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>88% (78%-95%)</td>
<td>91% (81%-97%)</td>
</tr>
<tr>
<td>Stringent CR</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>CR</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>VGPR</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>Partial response</td>
<td>24%</td>
<td>26%</td>
</tr>
</tbody>
</table>

*Based on treated patients.

REFERENCES

WARNINGS AND PRECAUTIONS
• Hypersensitivity and other administration reactions
• Neutropenia
• Thrombocytopenia
• Embryo-fetal toxicity
• Interference with crossmatching and red blood cell antibody screening

KEY COMPARISONS IN DARATUMUMAB MONOTHERAPY TRIAL

<table>
<thead>
<tr>
<th></th>
<th>Infusion time</th>
<th>Dose interruptions due to infusion-related reactions</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>34% of 258 patients</td>
<td>13% of 260 patients</td>
</tr>
<tr>
<td>Pharmacokinetics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean maximum trough concentrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>522 ± 226 µg/mL</td>
<td>593 ± 306 µg/mL</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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COVID-19 in the Clinic

Oncology Centers Examine the Aftermath of COVID-19 on Clinical Trials

by RACHEL NAROZNIAK, MA

FROM RESTRICTIONS IMPOSED BY pharmaceutical sponsors to suspensions and slowed enrollment, the coronavirus disease 2019 (COVID-19) has affected clinical trial operation in oncology centers across the country. Institutions are slowly but steadily resuming their investigational efforts, examining both their temporary and lasting effects the pandemic has left on their centers.

Declining accrual rates, delays in vital inclusion criteria testing, and social distancing protocols limiting the number of in-person office visits trials often require, are a few examples of the hurdles investigators are currently navigating as operations take steps toward the status quo. In interviews with OncologyLive®, investigators from several cancer centers provide insights on how their operations were affected and the strategies that could be sustained in the future.

MAKING UP FOR LOST TIME
In the earliest stages of the COVID-19 pandemic, investigators at the University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center in Pennsylvania preemptively paused patient enrollment in nontherapeutic clinical studies of pain management and palliative care interventions. Although therapeutic trials were largely permitted to continue accruing patients during this time, like other oncology institutions, UPMC Hillman Cancer Center faced pharmaceutical sponsor-issued limitations on new study initiation and patient enrollment.

“We suspended or reduced activity for around 80 trials over a 1- to 2-week period, and then we were able to reopen them with the help of our institutional review board,” said Robert L. Ferris, MD, PhD, director of UPMC Hillman Cancer Center. These impediments were further compounded by reduced clinic schedules and social distancing guidelines unique to the COVID-19 health crisis, culminating in a 20% to 30% decrease in accruals.

“Doctors weren’t seeing the same volume of patients, and due to social distancing, you can’t have all of the trials open that you would want to, and if primary care doctors’ offices are not open, then they’re not referring people to the oncologist [as frequently],” Ferris explained.

“Since we are over the peak now in western Pennsylvania, those 10 to 15 trials that were delayed until June have now opened. We see clinical trials as part of cancer treatment, so we’ve tried to keep as many open [as possible],” said Ferris, adding that as primary care doctors’ approach normal operation capacity, “we think we’ll make up that 20% to 30% decline.”

At COVID-19’s apex in mid-April, UPMC, the largest health care network in western Pennsylvania, allocated 2% of its total 5500 hospital beds and 48 of its 750 ventilators to patients with the novel respiratory virus, according to Steven Shapiro, MD, chief medical and scientific officer. On May 7, Shapiro attested that UPMC’s COVID-19-specific admissions have diminished.1

RESCRIPTING STANDARD PROCEDURE
As the number of cases continued to climb over April and May, investigators at Dana-Farber Cancer Institute and Mass General Cancer Center (Mass General), both in Boston, Massachusetts, not only saw a decline in accrual numbers, but also had to navigate the hurdles that came with cancelled qualifying procedures.

Following COVID-19’s spike in Massachusetts in late April,2 Dana-Farber has begun preparations for the return of elective procedures, which will directly benefit the studies that require preliminary biopsies. In early April, the COVID-19 pandemic inhibited Brigham and Women’s interventional radiologists, who perform more than 90% of Dana-Farber’s biopsies, from procuring tumor samples from patients, said Bruce...
E. Johnson, PhD, Dana-Farber’s chief clinical research officer.

“We do about 1000 research biopsies a year, or about 80 a month; it’s a very important scientific piece of what we do,” Johnson said. “On April 1, hospitals stopped doing elective biopsies, [causing us to go] from an average of 80 biopsies a month to 1 in April. This has affected us more than anything.”

Johnson recounted an instance when he was recently considering placing one of his patients on a clinical trial of a bispecific antibody, but was not able to do so, because the eligibility criteria mandated a biopsy to assess EGFR receptor presence on cancer cells.

“They wanted a biopsy so they could correlate the density of the receptors on the cells with how well the agent worked, and we were not able to put anybody on that study because it required the biopsy,” Johnson said. For Dana-Farber, hospitals’ reinstatement of elective procedures will result in a continuation of pretreatment specimen collection for patients who hope to participate in a study that requires one.

Despite COVID-19-related complications to clinical trial operation, preserving therapeutic studies has been, and remains, a key component of Dana-Farber’s clinical ethos, according to Johnson: “Sometimes, the best treatment for people with cancer is a clinical trial, so we were committed to making sure that people who were on a trial could continue on it. We were also committed to continuing to enroll patients onto trials, [while] being mindful of sponsor requirements and minimizing the exposure of our staff and patients to [COVID-19].”

Preliminary biopsies are just one of the study sponsor prerequisites that prompted consideration during the pandemic. Regarding pharmaceutical sponsors’ trial protocols, Johnson explained that the standard procedures for pharmacokinetic (PK) study procession also posed a challenge, due to the need for multiple patient visits. “The first day, patients start treatment, and then sometimes, they’ll come back for a day 5 or a week 1 [follow-up visit],” Johnson said.

Fortunately, through collaboration with its sponsors, Dana-Farber was able to temporarily waive these repeated trips to the center, as well as PK assessment in studies where PKs is not a primary safety end point.

As states including Massachusetts move to reopen, factors that could potentially limit a patient’s ability to participate in a clinical trial, such as biopsy collection, or have an impact on the aggregation of patient data are expected to have less of an effect on clinical trial operation at Dana-Farber, Johnson said. This sentiment is bolstered by the cancer center’s enrollment of patients on therapeutic studies through April.

“We keep close track of the number of people who enroll in therapeutic trials every month, and in 2018 and 2019, the median was about 200 patients a month. That started going down in early 2020, and we ended up putting 83 patients on protocol in April. Now you can think of that as a glass half full or half empty. It’s a little less than half of what we normally do, but we’re proud that we were able to maintain that through the month of April,” Johnson said.

The disruption to patient enrollment that Dana-Farber Cancer Institute and UPMC Hillman Cancer Center have encountered throughout the evolution of the COVID-19 pandemic is not specific to either institution. New data from the Cancer Research Institute and IQVIA show that just 20% of United States–based centers continued to enroll patients at the usual rate, while 20% halted new patient enrollment altogether. The hardship faced by oncology institutions globally mirrored that of United States oncology institutions: 20% of centers in Asia suspended enrollment, and although the European sites surveyed did not stop enrolling patients, 86% said the enrollments proceeded at a lower rate (FIGURE).

**FIGURE. COVID-19 Disrupts Clinical Trial Patient Enrollment Around the World (%)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Continued to enroll at same rate</th>
<th>Continued to enroll at a lower rate</th>
<th>Did not enroll</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>60%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Europe</td>
<td>86%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>60%</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

**STRATIFYING PATIENTS**

Mass General also saw a decline in patient accruals during the early evolution and peak of the COVID-19 pandemic, according to Rebecca Heist, MD, MPH, an expert in lung malignancies at the cancer center and an associate professor of medicine at Harvard Medical School. “New accrual numbers decreased significantly during this time, so we are planning now to expand those numbers,” Heist said.

At Mass General, clinical trial operations slowed, but never came to a full halt. “As a cancer center, it was really important to us to be able to continue to offer clinical trials for our patients, and we worked very hard to do that,” Heist said. “The only studies that were truly closed were [those for which] the sponsor suspended accrual,” she added.

During this time, the cancer center permitted patients who were already on clinical trials to continue receiving their investigational interventions and prioritized patient enrollment on therapeutic studies “with either potentially lifesaving or truly disease-altering treatments,” Heist explained. “There was a kind of self-regulation involved, where we knew that it wouldn’t be great for the system, operationally, if we flooded it with tons of new patient accruals because so many resources had to be redirected toward COVID-19,” she said.

As Mass General and other oncology institutions across the nation resume their clinical routine amid COVID-19, in the
context of its clinical study offerings, Mass General will continue to give preference to trials “with truly disease-altering potential.”

KEEP LIFESAVING OPTIONS ON THE TABLE
The practice of giving preference to the studies that may hold the most promise is not unique to Mass General. The Mayo Clinic Cancer Center adopted a similar approach, said Steven R. Alberts, MD, chair of the Division of Medical Oncology and deputy director for Clinical Research at the Mayo Clinic Cancer Center, which has sites in Rochester, Minnesota; Jacksonville, Florida; and Phoenix/Scottsdale, Arizona.

“Like any institution, COVID-19 certainly had a big impact on Mayo’s 3 main campuses in Minnesota, as well as in Phoenix and Jacksonville. When COVID-19 hit, it really caused us to greatly slow down our clinical trials,” Alberts said. “We didn’t put a complete stop to them, but it [prompted] us to look carefully at which trials were really critical to patients, and in general, our [feeling] was if there were no reasonable standard-of-care options for a patient, we would offer a clinical trial if that trial had some meaningful chance of benefiting a patient.”

During this period, Mayo Clinic halted translational data collection and primarily provided phase 2 and phase 3 trial offerings, and “very limited” phase 1 studies. In lieu of suspending studies, Mayo Clinic asked clinicians to internally consult with the clinical research chairs on a new patient enrollment to a given trial and obtain approval from the research chair. This method allowed Mayo Clinic to ensure that only patients who did not have viable therapeutic alternatives were being enrolled on the cancer center's clinical trials without wholly shutting down study operations. Unsurprisingly, Mayo Clinic saw a dip in patient accruals: “[at] the lowest point, our enrollment dropped to probably a third of our normal enrollment,” Alberts said.

In what was a welcome change to Mayo Clinic’s clinical milieu, the cancer center has resumed a more normalized state of study operation and began to open “most” of its clinical trials the week of May 11. Already, Mayo Clinic has seen an increase in the number of patients seeking care and clinical trial opportunities, according to Alberts. “We expected there to be some increase in patients coming back just for general care, including clinical trials, but our numbers have gone up more quickly than what we thought. At the end of this week, our normal volume of patients is at about 85% of what it had been prior to COVID-19, and if we add in the virtual visits, we’re up to about 95%, so the practice has ramped up very quickly, and along with that, we’re definitely seeing an increase in the number of patients going on to clinical trials,” Alberts said.

Moving forward, Mayo Clinic will continue to temporarily limit its menu of phase 1 studies that are visit or procedure intensive to minimize the number of patients who repeatedly come through the institution’s doors in this early stage of reopening, Alberts added.

FORGING AHEAD
Broadly, the clinicians agreed that although COVID-19 hindered some facets of study operation, they also indicated that some of the strategies that were implemented amid the pandemic could not only be sustained in the aftermath but also streamline the facilitation of clinical trials in the future.

“Like a lot of other large institutions, Mayo Clinic is slow to change and, and COVID-19 made us change very quickly in a lot of ways,” Alberts said. “The lessons [we] learned will help us design the next generation of trials.”

Specifically, the use of telemedicine and remote assessments, when possible, may allow cancer centers to reach a broader network of patients who might not have elected to pursue treatment at a certain institution due to distance, Alberts observed. In addition to the digital collection of data from study participants in the instances when it was feasible, Mayo Clinic also worked with the National Cancer Institute and pharmaceutical companies to ship drugs to patients within a prespecified radius. “In the past, nobody would have ever considered sending an oral drug to a patient on a clinical trial through the mail, outside some selected situations,” Alberts said, adding that akin to telehealth services, this practice could possibly endure.

At Mass General, virtual visits and evaluations have also been of value, especially in securing informed consent from patients who are about to enroll on a clinical trial, according to Heist, who said clinicians will video call patients and go page by page through the emailed consent form. “It’s something I would like to see continue after the pandemic,” Heist said. “It allows us to broaden access to patients, who are sometimes limited by the amount of travel that it takes to go on a clinical trial.”

Visiting the treating institution to physically sign the consent form and then subsequently returning for screening and treatment can be laborious and costly for patients at a distance from the cancer center, Heist explained. Obtaining consent remotely could reduce travel for study participants in the long run, minimizing the amount of travel that accompanies enrollment in a clinical trial. Acquiring consent electronically is also of interest at Dana-Farber, Johnson said.

In the months, and perhaps even the years to come, telemedicine will remain a key component of clinical trial coordination at UPMC Hillman Cancer Center, attested Ferris, who said the institution can be expected to take more advantage of remote monitoring in its commitment to affording its patients the timely care that they need, COVID-19 or no COVID-19. “We have to remind everybody that 700,000 or 800,000 people are going to die from cancer this year, so we believe continuing cancer treatment and research is crucial,” Ferris concluded.

REFERENCES
CALQUENCE® (ACALABRUTINIB): A BTK INHIBITOR FOR THE TREATMENT OF CLL/SLL

Appreciate the rapidly evolving treatment landscape in CLL

Explore BTK inhibition as an effective approach in CLL treatment

Assess recent phase 3 data in patients with previously untreated and with relapsed or refractory CLL

INDICATION AND USAGE
CALQUENCE is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

SELECT SAFETY INFORMATION
Serious adverse events, including fatal events, have occurred with CALQUENCE, including serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, and atrial fibrillation and flutter. The most common adverse reactions (≥ 30%) of any grade in patients with CLL were anemia, neutropenia, thrombocytopenia, headache, upper respiratory tract infection, and diarrhea.

PLEASE SEE BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION ON ADJACENT PAGES.

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

CLL, chronic lymphocytic leukemia; BTK, Bruton tyrosine kinase.
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CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Series and Opportunistic Infections
Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials, most of which were due to respiratory tract infections (11% of all patients, including pneumonia in 6%). These infections predominantly occurred in the absence of Grade 3-4 neutropenia, with neutropenic infection reported in 9% of all patients. Serious or Grade 3-4 neutropenia is a known consequence of CALQUENCE exposure, and includes, but is not limited to, hematopoietic virus reactivation, fungal pneumonia, Pneumocystis pneumonia, Epstein-Barr virus reactivation, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.

Use of anticoagulant agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 2.7% of patients taking CALQUENCE without anticoagulant agents and 3.6% of patients taking CALQUENCE with anticoagulant agents. Consider the risks and benefits of anticoagulant agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding. Consider the benefit-risk of withholding CALQUENCE for 5-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (22%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients with hematologic malignancies treated with CALQUENCE. Grade 4 neutropenia developed in 12% of patients. Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted [see Dose Modifications for Adverse Reactions (2.4) in the full Prescribing Information].

Second Primary Malignancies
Second primary malignancies, including skin cancers and other solid tumors, occurred in 12% of 1029 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was skin cancer; reported in 8% of patients. Monitor patients for skin cancers and advise protection from sun exposure.

Atrial Fibrillation and Flutter
Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmia, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dyspnea, syncope, dizziness) and manage as appropriate.

ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

• Serious and Opportunistic Infections [see Warnings and Precautions (5.1) in the full Prescribing Information]
• Hemorrhage [see Warnings and Precautions (5.2) in the full Prescribing Information]
• Cytopenias [see Warnings and Precautions (5.3) in the full Prescribing Information]
• Secondary Primary Malignancies [see Warnings and Precautions (5.4) in the full Prescribing Information]
• Atrial Fibrillation and Flutter [see Warnings and Precautions (5.5) in the full Prescribing Information]

Clinical Trials Experience
As 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 in the Warnings and Precautions reflect exposure to CALQUENCE 100 mg approximately every 12 hours in 1029 patients with hematologic malignancies. Treatment includes CALQUENCE monotherapy in 620 patients in 6 trials, and CALQUENCE with obinutuzumab in 209 patients in 2 trials. Among these patients, 60% of whom were ≥ 65 years of age with a total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance of 30 to 69 mL/min, hematologic malignancies included chronic lymphocytic leukemia, follicular lymphoma, and acute myeloid leukemia.

The safety of CALQUENCE plus obinutuzumab (CALQUENCE-G), CALQUENCE monotherapy, and obinutuzumab plus chlorambucil (CALQUENCE-G plus C) was evaluated in a randomized, open-label, active-controlled trial in 552 patients with previously untreated CLL or SLL (see Clinical Studies (4.2) in the full Prescribing Information).

Patients randomized to the CALQUENCE-G arm were treated with CALQUENCE 100 mg approximately every 12 hours until disease progression or unacceptable toxicity. Patients initiated obinutuzumab on Day 1 of Cycle 2, continuing for at least 5 cycles. Eligible patients were randomized to CALQUENCE monotherapy or CALQUENCE-G monotherapy, adjusted to CALQUENCE-G monotherapy received CALQUENCE approximately every 12 hours until disease progression or unacceptable toxicity. The trial required age < 65 years of age or 18 to < 65 years of age with a total Comorbidity Index Scale (CIRS) of 0 to 6; creatinine clearance of 60 to 90 mL/min, hepatic transaminases ≤ 3 times upper limit of normal (ULN) and total bilirubin ≤ 1.5 times ULN, and the ability to receive anti-CD20 agents other than rituximab or equivalent anti-idiotype antibodies.
**CALQUENCE® (acalabrutinib) capsules, for oral use**

**DOSAGE AND ADMINISTRATION**

Initial U.S. Approval: 2017

**Recommended Dosage**

For patients with previously untreated CLL or SLL, the recommended recommended dosage is 150 mg twice daily for 84 days (Cycle 1), followed by a 28-day drug-free period (Day 85 to Day 112), then repeated every 28 days. Start CALQUENCE at Cycle 2 for a total of 6 cycles of obinutuzumab. (See Table 3: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND).)

**Bioavailability**

CALQUENCE is rapidly and almost completely absorbed following oral administration.

**Pharmacokinetics**

Acalabrutinib is well absorbed when administered by mouth, with a median time to maximum plasma concentration (tmax) of less than 1 hour. Acalabrutinib is extensively metabolized, with a mean terminal elimination half-life (t1/2) of approximately 24 hours. Acalabrutinib and its major metabolite, M4 ([(2S)-2-(5,6,7,8-tetrahydro-4-propyl-4H-1-benzopyran-2-yl)acetyl]aminocarbonyl)alanine, are eliminated predominantly in feces (95%) and to a lesser extent in urine (5%).

**Table 1: Recommended Dose Modifications for Use with CYP3A Inhibitors or Inducers**

<table>
<thead>
<tr>
<th>CYP3A Co-administered</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate CYP3A</td>
<td>Dose modifications are not required for patients with mild or moderate hepatic impairment. The recommended dose of CALQUENCE is 150 mg twice daily.</td>
</tr>
<tr>
<td>Severe CYP3A</td>
<td>Dose modifications are not required for patients with mild or moderate hepatic impairment. The recommended dose of CALQUENCE is 150 mg twice daily.</td>
</tr>
<tr>
<td>Strong CYP3A</td>
<td>Dose modifications are not required for patients with mild or moderate hepatic impairment. The recommended dose of CALQUENCE is 150 mg twice daily.</td>
</tr>
</tbody>
</table>

**Table 2: Select Non-Hematologic Laboratory Abnormalities (≥ 10% Any Grade), New or Worse from Baseline in Patients Receiving CALQUENCE (ELEVATE-TN)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade (≥ 10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>51.9</td>
<td>5.2</td>
<td>0.3</td>
<td>0.0</td>
<td>58.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20.7</td>
<td>1.2</td>
<td>0.1</td>
<td>0.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15.9</td>
<td>0.6</td>
<td>0.0</td>
<td>0.0</td>
<td>16.5</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>11.0</td>
<td>0.6</td>
<td>0.0</td>
<td>0.0</td>
<td>11.6</td>
</tr>
</tbody>
</table>

**Acalabrutinib and Its Active Metabolite Excreted in Breast Milk**

Acalabrutinib and its active metabolite (M4) were detected in the breast milk of a breastfeeding woman following administration of a single 150 mg dose of CALQUENCE. Acalabrutinib and its active metabolite were present in breast milk. Breastfeeding is not recommended during treatment with CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose. This drug is excreted in breast milk, and its effects on the breastfed child, or on milk production have not been evaluated.

**Females and Males of Reproductive Potential**

- **Pregnancy**
  - Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.
  - Females of reproductive potential should use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE.
- **Contraception**
  - Females of reproductive potential should use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE.

**Table 3: Common Adverse Reactions (≥ 15% Any Grade) with CALQUENCE in Patients with CLL (ASCEND)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade (≥ 15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>15.9</td>
<td>1.2</td>
<td>0.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Peptide (2%, 2, 1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Reactions**

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE (CALQUENCE in combination with obinutuzumab and monotherapy) included:

- Myelosuppression: second primary malignancy (10%), non-melanoma skin cancer (5%)
- Cardiac disorders: atrial fibrillation or flutter (3.6%), hypertension (5%)
- Infection: herpesvirus infection (5%)

**Risk Summary**

- **Females of Reproductive Potential**
  - Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.
  - Females of reproductive potential should use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE.

**Contraception**

- **Pregnancy**
  - Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy.
  - Females of reproductive potential should use effective contraception during treatment with CALQUENCE and for at least 1 week following the last dose of CALQUENCE.

**Adverse Reactions**

Other clinically relevant adverse reactions (all grades incidence < 15%) in recipients of CALQUENCE included:

- Skin and cutaneous disorders: bruising (10%), rash (9%)
- Myelosuppression: second primary malignancy (12%), non-melanoma skin cancer (9%)
- Musculoskeletal and connective tissue disorders: arthralgia (9%)
- Cardiovascular disorders: atrial fibrillation or flutter (5%), hypertension (3.2%)
- Infections: herpesvirus infection (3.6%)
@OncLive
The oncology drug pacritinib, an investigational JAK2, IRAK1, and CSF1R inhibitor, is being explored in the phase 3 PRE-VENT trial as a treatment for cytokine storm in hospitalized patients with severe COVID-19. #coronavirus #COVID19 onclive.com/link/7901

@OncLive
BREAKING: @US_FDA Approves Niraparib for Frontline Maintenance in Ovarian Cancer onclive.com/link/7902

@OncLive
Olaparib Pivotal mCRPC Data Published in @NEJM as @US_FDA Weighs Approval #pcsm onclive.com/link/7903

@OncLive
COVID-19 Causes Major Treatment Modifications in Head and Neck Cancer @DrNabilSaba @WinshipAtEmory #coronavirus #COVID19 onclive.com/link/7904

@OncLive
The PD-1 inhibitor cemiplimab significantly improved OS versus platinum-based chemotherapy as a frontline treatment for patients with locally advanced or metastatic NSCLC and a PD-L1 expression level of at least 50%. #lcsm onclive.com/link/7906

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SONPAVDE NAVIGATES NEWFOUND GU CANCER TREATMENT CONSIDERATIONS AMID COVID-19 CRISIS
Guru P. Sonpavde, MD, director of the bladder cancer program at Dana-Farber Cancer Institute in Boston, Massachusetts, highlights how coronavirus disease 2019 (COVID-19) has affected the dosing and scheduling of chemotherapy, immunotherapy, and targeted therapy for patients with bladder cancer.

FDA APPROVAL INSIGHTS: SACITUZUMAB GOVITECAN IN mTNBC
Aditya Bardia, MD, MPH, director of precision medicine at the Center for Breast Cancer and founding director of the Molecular and Precision Medicine Metastatic Breast Cancer Clinic at Massachusetts General Hospital Cancer Center in Boston, discusses the implications of the approval of sacituzumab govitacan-hziy (Trodelvy) in metastatic triple-negative breast cancer (mTNBC).

PETRYLAK ON EV-103 FINDINGS
In the phase 1b/2 EV-103 trial (NCT03288545), the combination of enfortumab vedotin-ejfv (Padcev) and pembrolizumab (Keytruda) led to a tumor shrinkage rate of 90% in patients with locally advanced or metastatic urothelial cancer, according to Daniel P. Petrylak, MD, professor of medicine and urology and coleader of Cancer Signaling Networks at Yale Cancer Center in New Haven, Connecticut.

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INCORPORATING TELEMEDICINE AS PART OF COVID-19 OUTBREAK RESPONSE SYSTEMS
Health care providers should revisit disaster response policies to incorporate telemedicine systems to address some of the unique challenges posed by infectious disease outbreaks such as the coronavirus disease 2019 (COVID-19). As COVID-19 threatens to overwhelm the US health care system and supply chains, telemedicine systems can be used to prevent overcrowding while limiting human exposure to the virus and facilitating high-quality care.


COVID-19 Pandemic Prompts New Transplant Concerns in Hematologic Malignancies
Interview with NAVAL G. DAVER, MD

NAVAL G. DAVER, MD

IN LIGHT OF THE coronavirus disease 2019 (COVID-19) pandemic, transplant-eligible patients with cancer are undergoing careful assessment to determine whether they should move forward with the procedure or receive additional consolidation therapy to buy time, according to Naval G. Daver, MD, associate professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston. For patients with hematologic malignancies such as acute myeloid leukemia or acute lymphocytic leukemia, most allogeneic stem cell transplants in the frontline setting are being conducted as planned, Daver said, although patients will be tested for the virus to ensure they are not infected prior to the procedure. If the test results are negative, the procedure is typically conducted.

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MJH LIFE SCIENCES™ NEWS NETWORK LAUNCHES
On April 2, 2020, MJH Life Sciences™ demonstrated its commitment to delivering timely, up-to-date information to clinicians by rolling out its comprehensive, 24-hour MJH Life Sciences™ News Network. Offering around-the-clock coverage on clinical developments and advancements, the network is accessible across all of MJH’s branded websites, including OncLive.com, and can be found on the bottom left corner of your screen.

NOTABLE QUOTABLES

“[Genetic testing] is going to prevent a large number of cancers or [help us] identify them at an earlier or more treatable stage. Genetic testing needs to be [performed] much more than it is now.”

—Kevin Hughes, MD
Medical Director, Bermuda Cancer Genetics and Risk Assessment Clinic; Codirector, Avon Breast Evaluation Program, Massachusetts General Hospital

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“As oncologists, we often rely on guidelines to make treatment decisions.... However, none of those guidelines include dealing with a pandemic such as COVID-19 [coronavirus disease 2019].”

—Narjust Duma, MD
Assistant Professor, Division of Hematology, Medical Oncology and Palliative Care, Department of Medicine, University of Wisconsin–Madison

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AI Makes Inroads Into Oncology Practice

by DENISE MYSHKO

Oncology practices large and small are starting to tap into the power of data analytics and artificial intelligence (AI) to help identify patients at risk of relapse or adverse effects (AEs) and to assist in making clinical decisions on care. Informatic tools are now using predictive analytics and evidenced-based mechanisms, and these are being combined with electronic health records (EHRs) to bring the power of big data to daily practice.

Although the impact of these systems is just starting to be felt in the oncology field, tools that support routine clinical decisions and genomic risk stratification are likely to be adopted more broadly within the next several years. Experts say this is a trend that promises to dramatically change the way care is practiced and delivered.

Potential uses for AI systems that could affect decisions on cancer care for individual patients include predicting the risk of AEs from chemotherapy, the likely duration of response from chemotherapy, recurrence risk, and overall life expectancy. Systems that incorporate evidenced-based mechanisms or predictive analytics can also help deliver value-based care and reduce the risk of hospitalization due to AEs, proponents say.

The trend toward alternative payment models that are focused on value is going to help drive the adoption of these tools, James Hamrick, MD, senior medical director at Flatiron Health, an oncology technology and research company, said in an interview with OncologyLive®.

“There is some appetite to pay for [these tools] but I think practices and hospitals are appropriately conservative. These are sophisticated tools so they have to work and deliver value.”

The power of using big data goes beyond immediate clinical utility, said Debra Patt, MD, PhD, MBA, a breast cancer specialist who is executive vice president at Texas Oncology in Austin, part of the US Oncology Network. “When you have practice management systems integrated with electronic health records integrating with research platforms, you can get information that allows you to make better decisions about all aspects of care delivery.”

Data-driven algorithms that would be meaningful in clinical practice are part of a robust AI sector in health care. The market is valued at $5.9 billion this year and is forecast to grow to $31.3 billion in revenue by 2025, according to Grand View Research, an industry analytics company headquartered in San Francisco, California.

In oncology, a range of applications are being developed. For example, COTA, a health care technology company based in Boston, Massachusetts, has created a tool that helps cancer centers correlate care patterns with outcomes. The system can help center directors understand patient populations and treatment patterns.

Called Real-World Analytics (RWA), the program collects clinical data from EHRs and extracts outcomes from this information. It allows centers to view specific care delivery trends, such as progression-free survival and overall survival. COTA now is working to add cost data to the system.

“It’s not unusual for centers to not fully understand what types of patients they see and the specific characteristics of those...
has been established through the digitalization of medical records, the availability of data storage in the cloud, software advancements, and mobile technologies. In oncology, evidenced-based AI tools are starting to be used in 3 key areas: population health management, radiomics, and pathology. Patt said many tools can now model the outcomes of patient visits to the emergency department and hospitalizations but the challenge is how to make that information meaningful operationally. Other challenges involving data collection and analytical bias exist as well (FIGURE). Predictive analytics is expected to allow clinicians to understand up front the patients who are more likely to experience AEs.

“As oncologists, we live in a reactive world,” Hamrick said. “The only time I have insight into what is going on with a patient is when they are in my office, or perhaps when I hear that they landed in the emergency room or hospital. For the patient, the journey is every day. They are dealing with the physical, financial, and emotional toxicity of their cancer. ... If we can understand at the beginning of chemotherapy what are the factors that make it likely that this patient may wind up in the emergency [department], then we can shift resources and interventions so we can move from reactive to proactive.”

Technology companies and larger hospital systems are beginning to develop the tools that will allow these types of analyses. The task is Herculean, as research conducted by a team of Google and academic researchers shows. Their predictive modeling study used deidentified EHR data from patients hospitalized at 2 US medical centers for at least 24 hours and found nearly 47 billion data points—an average of more than 200,000 per person—for characteristics such as demographics, provider orders, diagnoses, procedures, medications, laboratory values, vital signs, and clinical notes.

At Memorial Sloan Kettering Cancer Center (MSK), investigators developed a risk model that used its own EHR data to identify patients at high risk for a potentially preventable acute care visit.

“We wanted to identify those patients we thought would most benefit from intensive monitoring between clinic visits to be able to actively intervene for those patients and help mitigate their suffering and symptoms,” Robert Daly, MD, MBA, medical oncologist at MSK in New York, New York, said in an interview. MSK conducted a pilot program from January 2014 to September 2018 using a model that was built internally using 270 observation-level features from electronic medical record data collected from the initial visit to the first antineoplastic order. Features were grouped into categories that included sociodemographic data, malignancy and treatment characteristics, laboratory results, medical and social history, medications, and prior MSK acute care encounters. The model helped to identify the patients who accounted for 35% of potentially preventable acute care visits and 51% of the inpatient beds used by the cohort.

Isaac Wagner, senior director of strategy analytics at MSK, said the decision to create their own analytics tool was based on the fact that they were trying to address a specific problem: identify patients with toxicity to chemotherapy for an intensive monitoring program.

“I haven’t seen any product that solves this problem,” he said in an interview. “For us, some of the most useful data were from custom forms we created ourselves. A vendor is likely to use data that everyone has in their system in the same way and that could miss a lot of things. There is also the component of speed. We didn’t just want to use claims data. It had to be data that are available before the clinical decision.”

Moving forward, Daly said the center is looking at how to best incorporate the risk model into decision-making and scale the monitoring program. “The model predicts risk at an initial point in time before the patient starts the first treatment,” he said.

“We heard from many physicians and nurses that they would like to see a more iterative risk model over the course of the patient’s treatment and then make a...
at the point of the care to enable decisions that are backed by guidelines and published evidence; however, most EHR systems do not have this information embedded into them.11

The American Society of Clinical Oncology (ASCO) is trying to address some of these issues with CancerLinQ, which collects and analyzes real-world cancer care data from cancer centers and oncology practices across the United States. CancerLinQ currently has more than 100 subscribers, and 60 practices have completed the onboarding process to establish a link between the CancerLinQ database and their EHR system.12

The promise of CancerLinQ is to be able to collate real-world patient data, including outcomes, so that assessments can be made about treatment for current patients, Barbara L. McAneny, MD, a medical oncologist/hematologist who is chief executive officer of New Mexico Cancer Center in Albuquerque, said in an interview.

“Clinical trials require that patients be triathletes with cancer, with no other conditions, no other previous cancers, promising to be completely compliant and sufficiently affluent that they can afford to travel to a university setting to participate in a clinical trial,” said McAneny, who formerly served as president of the American Medical Association. “That is not the population we treat. We treat people who are human beings, with all their foibles. They are not always compliant, they lack resources, they skip appointments, they have diabetes and hypertension and heart problems and elevated creatinine—all the things that would exclude them from a clinical trial.”

McAneny said ASCO needs to address some issues that make it difficult to use CancerLinQ as a resource at the point of care. One concern is how physicians upload data. “If busy physicians struggling to keep up with their work have to enter data, it isn’t going to happen. If practices have to pay somebody to do data entry, it isn’t going to happen. ASCO has made great strides in this. But we aren’t entirely there.”

Additionally, she said, querying the database should be easier. “On a day when I am seeing 25 to 35 patients, I don’t have time to take an hour to query a database and sort through for an answer. I need to have simple questions answered, for example, how many people with this regimen also have these other problems. If I can do that, ideally with the patient in the room, then you have a tool that is really going to change how care is delivered.”

Robert S. Miller, MD, medical director at CancerLinQ, said via email that the organization is working to address such concerns. CancerLinQ is continually adding usable cases—information from more than 1.5 million patients with cancer as of the end of April—to the CancerLinQ database, up from 1.4 million patient records at the end of 2019.

“These cases reflect the diversity of cancer care throughout the United States—urban, rural, and suburban settings; smaller community practices, hospital/health systems, and large academic medical centers, including a growing number of NCI [National Cancer Institute]-designated cancer centers—patients ranging from very young to seniors, every racial/ethnic population, and individuals of all different health statuses,” Miller said.

He said ASCO recognizes the challenges of EHR compatibility. There are more than 1500 EHR systems available today and few are fully compatible with one another. To address this, ASCO launched the Minimal Common Oncology Data Elements initiative in collaboration with the MITRE Corporation, the ASCO Foundation, the Alliance for Clinical Trials in Oncology, and the American Society for Radiation Oncology. Version 1.0 of the Minimal Common Oncology Data Elements rolled out in March 2020 and the data elements are available for use free of charge.

Others are attempting to address the issue of interoperability as well. Flatiron, for example, launched a clinical decision support and pathways tool, called Flatiron Assist, in October 2019; so far, the tool is being used in 1 hospital system and 3 community oncology practices. Flatiron Assist is integrated into OncoEMR, Flatiron’s EHR system, and available in EPIC. The system pulls available demographics, diagnosis, and cancer-specific data from the electronic record and provides therapy options based on National Comprehensive Cancer Network guidelines and practice preferences. It also identifies clinical trials that might match the patients’ needs.13

Clinical decision support tools embedded in EHRs can reduce the variability of care
and increase compliance with evidence-based decision-making. US Oncology, for example, said its decision support tool had improved compliance from 58% to 72%.

“We think cancer patients are better served when they are treated by evidenced-based guidelines, recognizing there are all sorts of reasons for warranted variation from guidelines,” Patt said. US Oncology, part of McKesson, implemented McKesson’s Clear Value Plus through its EHR. Patt said the network had previously used a system for value-based care assessments but it was not embedded in the electronic record.

Clear Value Plus provides information about National Comprehensive Cancer Network guidelines within the clinical workflow, along with financial information, real-time reporting and benchmarking, and an interface with the EHR.14

“This is really useful for me because when I am in front of patients discussing chemotherapy and their options, I can pull up the regimens and show them to patients,” Patt said. “I use that to help facilitate prescribing. That decision support system not only facilitates my compliance with evidence-based treatment, but it also engages in an education tool that is very specific for the patient. This can create a document for the patient that can help them understand their cancer and improve their own health literacy.”

Page, of CCBD, said that prior to implementing the ClinicalPath system, the physicians at his practice were not consistent in terms of the treatment regimens used. “We had over a thousand chemotherapy regimens and every doctor had his or her own nuance of how they would dose the drugs, sequence the drugs, use different supportive care drugs, and with a variety of treatment schedules.”

Elsevier’s ClinicalPath, formerly Via Oncology, delivers oncology pathways synthesized from evidence in the literature. ClinicalPath covers more than 97% of cancer cases in medical and radiation oncology and is delivered at the point of care through integration with leading EHR technologies.15

The pathways take into account patient-specific information, including cancer stage, labs, biomarkers, and patient preferences, among other data elements, Richard Loomis, MD, chief informatics officer at Elsevier, said in an interview. “It works to determine the most current and appropriate evidence-based treatment for that particular patient. It is really intended to be a guide and to help drive decision-making at the point of care to reduce variability.”

Page said ClinicalPath also provides financial efficiencies for practices.

“The pharmacy is able to more predictively purchase drugs and more consistently mix drugs, and this creates a lot of efficiencies, and improves patient safety,” Page said. “We’ve also used those treatment pathways in order to negotiate value-based insurance contracts. We work with big payers like Aetna to use pathway compliance as a model for shared savings.”

CCBD has better than 80% compliance in meeting the prescribed pathways, Page said. “There are so many new drugs and new indications and combinations that your typical community oncologist cannot keep up with everything. The assistance of a pathway system helps to keep us abreast of the latest evidence-based treatments that are out there.”

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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 with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may
NUBEQA®—Focus on both MFS and tolerability\(^1,2\)

**40 MONTHS**

More than double the median MFS with NUBEQA + ADT* vs 18 months with ADT alone\(^1\)

(\(HR: 0.41; 95\% CI: 0.34-0.50; P=0.0001\))

**PROVEN TOLERABILITY**

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%)

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.

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%).

**SAME RATE OF PERMANENT DISCONTINUATION**

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. 1509 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, \(^{99m}\)Tc bone scan by BICR, unacceptable toxicity, or withdrawal. OS data were not mature at the time of final MFS analysis (57% of the required number of events)\(^1,2\). The planned final OS analysis has been conducted and mature data on OS will be presented at an upcoming scientific meeting.

\(^*\)NUBEQA + ADT, 95% CI: 34.3-NR. \(^\text{†}\)ADT alone, 95% CI: 15.5-22.3.

Start new patients with up to 2 months free.\(^\text{‡}\)

Visit NUBEQAhcp.com

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 NUPEQA (darolutamide) 300 mg tablets

Please see the following page for brief summary of full Prescribing Information.

---

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 1-833-337-3833 or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions.

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; NR=not reached; GnRH=gonadotropin-releasing hormone; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging; OS=overall survival.

\(^\text{‡}\)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 1-833-337-3833 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 (mCRPC).  

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)].  
Advise males 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, 8.3)].  

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.  
ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (mCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.  
Overall, 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 included 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.  
Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).  
Dose interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).  
Dose reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).  
Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.  

Table 1: Adverse Reactions in ARAMIS  
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
<th>All Grades</th>
<th>Grades ≥ 3</th>
<th>All Grades</th>
<th>Grades ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>6</td>
<td>16</td>
<td>16</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia  
2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.  

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.  

References:  
For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937.

7.2 Effects of NUBEQA on Other Drugs  
Breast Cancer Resistance Protein (BCRP) Substrates  
NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.  

8 USE IN SPECIFIC POPULATIONS  
8.1 Pregnancy  
See Warnings and Precautions.  

Risk Summary  
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 [see Clinical Pharmacology (12.1)]. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.  

8.2 Lactation  
See Warnings and Precautions.  

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)].  
Involatility  
Males  
Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].  

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. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.  

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.

1 The denomenator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.  
2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
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, hypospermatia, 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 (2.7)].
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)].

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6711000BS

Continuous Dabrafenib/Trametinib Dosing Improves PFS in BRAF+ Melanoma

by JASON M. BRODERICK

CONTINUOUS DOSING WITH DABRAFENIB (Tafinlar) and trametinib (Mekinist) improved progression-free survival (PFS) compared with intermittent dosing in patients with BRAF mutation-positive advanced melanoma, according to results from the phase 2 SWOG S1320 trial.\(^1\)

Data presented during the 2020 American Association for Cancer Research Virtual Annual Meeting I showed that the median PFS was 9.0 months in the continuous arm versus 5.5 months in the intermittent arm (HR, 1.36; 80% CI, 1.10-1.66; \(P = .063\)).

“The PFS advantage in favor of continuous dosing was observed in younger and older patients, men and women, patients with and without prior immune checkpoint inhibitor therapy, and in patients with normal and elevated baseline LDH [lactate dehydrogenase] levels,” said Alain Algazi, MD, an associate professor in the Department of Medicine at University of California San Francisco and the study chair with SWOG Cancer Research Network, which led the research.

The outcome of the trial was the opposite of the study hypothesis. Based on positive preclinical signals in mouse models, the investigators hypothesized that intermittent dosing of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib could overcome acquired resistance to BRAF inhibitors and improve PFS in this patient population.

The open-label phase 2 SWOG S1320 trial (NCT02196181) enrolled 206 patients with advanced BRAF V600E/K-positive melanoma over 5 years at 68 clinical sites, including some community practices. Baseline characteristics were well balanced between the 2 treatment arms. The median age was 58 and 62 years in the continuous and intermittent arms, respectively. Fifty-nine percent and 69% of patients were male, and 98% and 97% of patients were white in the 2 arms, respectively. Almost all patients in each arm had an ECOG performance status of 0 or 1. Seventy percent of patients in each arm had no prior exposure to an immune checkpoint inhibitor.

All patients received an 8-week lead-in course of continuous dosing after which patients who achieved an objective response or stable disease were randomized to continuous (n = 105) or intermittent (n = 101) dabrafenib plus trametinib. The intermittent schedule was 3 weeks off/5 weeks on. Algazi noted that following the 8-week lead-in period, “There were no statistically significant differences in the initial tumor response between the 2 treatment arms.”

In the continuous arm, 21 patients remained on treatment at the time of the analysis, with 84 patients having discontinued, primarily due to disease progression (n = 54). In the intermittent cohort, 17 patients were still on treatment, with 84 discontinuing, again primarily due to progression (n = 62).

Although the study was not powered to detect differences in overall survival (OS), Algazi reported that there was no significant difference in survival observed, with a median OS of 29.2 months in each arm. This lack of OS difference extended across all key patient subgroups.

However, Algazi noted that, “The shorter period of disease control in intermittent-dosed patients appeared to be offset after disease progression in S1320.” Following disease progression, there was a statistically significant OS improvement favoring
Addressing potential explanations for this outcome, Algazi discussed subsequent therapy, explaining that investigator-reported data showed that about half of the patients in each arm received an immunotherapy agent post S1320. “There was no significant difference in exposure to anti-CTLA-04 or anti-PD-1 antibodies following treatment on S1320 between the 2 study arms.” Thus, subsequent immunotherapy would not explain the OS difference.

Additionally, he also recalled that since “30% of patients in each study arm were exposed to immune checkpoint inhibitors prior to study enrollment, any latent effect of prior exposure to these agents is unlikely to explain differences in post-study survival.”

Regarding the OS data, Algazi cautioned, “While interesting, OS or postprogression survival findings should be considered hypothesis-generating at this point.”

Discussing the safety data in the S1320 trial, Algazi said, “We observed similar toxicity in both arms, despite decreased drug exposure in the intermittent arm.”

The most common treatment-related adverse events were chills, fatigue, and fever. Grade 1/2 chills occurred in 30 patients in the continuous arm versus 32 patients in the intermittent arm, grade 1/2 fatigue occurred in 50 patients in both arms, and grade 1/2 fever occurred in 37 patients in the continuous arm versus 31 patients in the intermittent arm.

There was 1 case each of grade 3 chills in both arms. Grade 3 fatigue occurred in 8 patients and 3 patients in the continuous and intermittent arms, respectively. There were 6 patients with grade 3 fever in the continuous arm and 1 patient in the intermittent arm had grade 4 fever.

Algazi offered several potential explanations for why the trial was a “negative” trial (FIGURE 1); 1 reason was because there was less drug exposure in patients randomized to the intermittent-dosing arm. “But this was also true in the animal model of vemurafenib,” he noted. “And if this is a major differentiating factor, we have to assume that any benefit of intermittent therapy could not offset decreased drug exposure.”

He also offered that, “There are preclinical data suggesting that a rapid decrement in drug levels is required to get effective tumor killing in drug-addicted cells. The long half-life of trametinib—4 days in humans—may have precluded the rapid decrement in exposure required to get an effective drug withdrawal.”

A third explanation postulated by Algazi was that in these patients, non-MAPK resistance pathways may be the real issue. “It is possible that mechanisms that can be addressed with intermittent dosing are not the predominant mechanisms of treatment resistance in a broad human patient population.”

And the final hypothesis Algazi gave for the unexpected study outcome was that “it may take longer than 8 weeks for resistant clones to develop.”

Also commenting on the outcomes in a press release was Antoni Ribas, MD, PhD, the senior leader on the trial, the former chair of the melanoma research committee at SWOG, and the American Association for Cancer Research president. He is also a professor of medicine at the David Geffen School of Medicine at the University of California Los Angeles (UCLA), director of the UCLA Jonsson Comprehensive Cancer Center Tumor Immunology Program, and director of the Parker Institute for Cancer Immunotherapy Center at UCLA.3

“The idea of prescribing therapy intermittently made sense,” Ribas stated. “Cancer cells wouldn’t have enough time to get used to it and become resistant—a notion that was supported scientifically by well-conducted studies in the laboratory. This clinical study illustrates the importance of ultimately testing hypotheses in human patients, which is the underlying reason for the existence of NCI [National Cancer Institute]-funded groups like SWOG.”

REFERENCES
1. Algazi A, Othus M, Daud A, et al. SWOG S1320: improved progression-free survival with continuous compared to intermittent dosing with dabrafenib and trametinib in patients with BRAF mutation–positive advanced melanoma. Alain Algazi, MD, offered observations on the “negative” results:
   - Less drug exposure in patients randomized to the intermittent-dosing arm
   - The long half-life of trametinib may have precluded the rapid decrement in exposure required to get an effective drug withdrawal
   - Non-MAPK resistance pathways
   - Timeline for resistant clone development was not long enough

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Talazoparib Improves QOL, But Not OS in Advanced BRCA1/2+ Breast Cancer

by JASON HARRIS

TREATMENT WITH TALAZOPARIB (TALZENNA) did not demonstrate a statistically significant overall survival (OS) benefit in patients with BRCA1/2-mutated metastatic HER2-negative breast cancer, according to updated findings from the phase 3 EMBRACA trial (NCT01945775). However, lead author Jennifer K. Litton, MD, said that there is still reason to believe treatment with the PARP inhibitor can improve OS.

“In patients with germline BRCA1/2-mutated advanced breast cancer, talazoparib did not [show a] statistically significant improvement in OS compared with chemotherapy,” said Litton, professor of breast medical oncology at The University of Texas MD Anderson Cancer Center, who presented the results during the 2020 American Association for Cancer Research Virtual Annual Meeting I. “It is important to note that most patients in the study went on to receive subsequent therapies, which may have confounded the survival analysis.”

The FDA approved talazoparib in 2018 for adults with germline BRCA1/2-mutant, HER2-negative locally advanced or metastatic breast cancer based on previously published results from the EMBRACA trial, which showed that the drug was associated with a 3.0-month improvement in median progression-free survival (PFS). At a median follow-up of 11.2 months, the median PFS was 8.6 months with talazoparib versus 5.6 months (95% CI, 4.2-6.7) with chemotherapy (HR, 0.54; 95% CI, 0.41-0.71; P <.0001). The PFS benefit with talazoparib was seen across all predetermined patient subgroups.

In EMBRACA, patients were assigned to 1 mg daily of oral talazoparib (n = 287) or physician’s choice of capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles (n = 144). Eligible patients had received no more than 3 previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated.

Investigators observed no statistically significant difference in median OS between the talazoparib and chemotherapy arms (19.3 vs 19.5 months, respectively; HR, 0.820; 95% bootstrap CI, 0.503-1.029) or PARP inhibition alone (19.3 vs 19.1 months, respectively; HR, 0.820; 95% bootstrap CI, 0.617-1.047).

“The hazard ratio and 95% confidence intervals obtained for OS after dose adjustment for subsequent platinum and/or PARP inhibition suggest that the primary OS analysis underestimated the treatment benefit of talazoparib,” Litton said.

TALAZOPARIB IMPROVES QOL

Investigators observed a statistically significant improvement in the estimated change in baseline global health status/quality of life (QOL) in patients treated with talazoparib (2.1; 95% CI, 0.1-4.1) compared with chemotherapy (−5.7; 95% CI, −10.0 to −1.4).

“Compared with chemotherapy, treatment with talazoparib was associated with a significant delay in the time to definitive clinically meaningful deterioration in the quality-of-life scores,” Litton said.

Furthermore, talazoparib was well tolerated. Approximately 35% of patients in the experimental arm experienced serious OS still did not reach statistical significance compared with chemotherapy in patients who received subsequent PARP inhibitor and/or platinum therapy (19.3 vs 17.4 months, respectively; HR, 0.756; 95% bootstrap CI, 0.503-1.029) or PARP inhibition alone (19.3 vs 19.1 months, respectively; HR, 0.820; 95% bootstrap CI, 0.617-1.047).

Investigators performed the final OS analysis using the intention-to-treat population after observing 324 deaths. After a median follow-up of 44.9 months for talazoparib and 36.8 months for chemotherapy, 216 patients in the talazoparib group and 108 patients in the chemotherapy group had died.

Overall, 48.4% of patients in the experimental arm and 59.7% of patients in the control arm went on to receive subsequent treatment with a PARP inhibitor or platinum-based chemotherapy. Of those who received subsequent treatment, 46.3% in the talazoparib group and 41.7% in the chemotherapy group received platinum therapy.

Litton said that adjusting for poststudy chemotherapy for subsequent platinum and/or PARP inhibition suggest that the primary OS analysis underestimated the treatment benefit of talazoparib,” Litton said.

**TABLE.** Updated Results From the Phase 3 EMBRACA Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Talazoparib (n = 287)</th>
<th>Chemotherapy (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>8.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>19.3</td>
<td>19.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.848 (0.670-1.073); P = .17</td>
<td></td>
</tr>
<tr>
<td>Change in baseline QOL (95% CI)</td>
<td>2.1 (0.1-4.1)</td>
<td>-5.7 (-10.0 to -1.4)</td>
</tr>
</tbody>
</table>

**Subsequent therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Talazoparib (n = 139)</th>
<th>Chemotherapy (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARP inhibitor (%)</td>
<td>4.5%</td>
<td>32.6%</td>
</tr>
<tr>
<td>Platinum-based chemotherapy (%)</td>
<td>46.3%</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival; QOL, quality of life.
In the talazoparib arm, 56.3% of patients experienced grade 3/4 hematological AEs compared with 38.1% of patients assigned to chemotherapy. Most grade 3/4 hematological AEs reported in the talazoparib group were successfully managed with supportive care and dose modifications.

In the talazoparib arm, 56.3% of patients experienced grade 3/4 hematological AEs compared with 38.1% of patients assigned to chemotherapy. Most grade 3/4 hematological AEs reported in the talazoparib group were successfully managed with supportive care and dose modifications.
Atezolizumab Plus Vemurafenib/Cobimetinib Impresses in BRAF V600+ Melanoma

by KRISTI ROSA

TREATMENT WITH ATEZOLIZUMAB (Tecentriq) in combination with vemurafenib (Zelboraf) and cobimetinib (Cotellic) was found to significantly improve progression-free survival (PFS) and produce durable responses versus vemurafenib and cobimetinib alone in treatment-naive patients with BRAF V600-mutant advanced melanoma, according to data from the phase 3 IMspire150 trial presented at the 2020 American Association for Cancer Research Virtual Annual Meeting I.

“Atezolizumab combined with vemurafenib and cobimetinib showed a statistically significant and clinically meaningful [improvement] in PFS via investigator assessment when compared with placebo plus vemurafenib and cobimetinib. At the time of this analysis, the overall survival [OS] data are not mature, but did favor the atezolizumab arm,” said lead study author Grant A. McArthur, MBBS, PhD, executive director of the Victorian Comprehensive Cancer Centre, inaugural Lorenzo Galli Chair of Melanoma and Skin Cancers at the University of Melbourne, and a senior principal research fellow.

Specifically, the investigator-assessed median PFS with the triplet was 15.1 months (95% CI, 11.4-18.4) versus 10.6 months with vemurafenib/cobimetinib alone (95% CI, 9.3-12.7; log-rank P = .0249); this effect was observed across all prognostic subgroups. Furthermore, the median PFS, when assessed by an independent review committee (IRC), was 16.1 months (95% CI, 11.3-18.5) and 12.3 months (95% CI, 10.8-14.7) with the triplet and the doublet, respectively (log-rank P = .1607).

“Importantly, the addition of atezolizumab to vemurafenib and cobimetinib provided a clinically meaningful improvement in duration of response compared with vemurafenib and cobimetinib alone,” added McArthur, who is also head of the Molecular Oncology Laboratory and of the Cancer Therapeutics Program, Cancer Research, and a senior consultant medical oncologist, Cancer Medicine, at the Peter MacCallum Cancer Centre. “Overall, the safety profile was consistent with the known risks for each individual study drug and the vemurafenib plus cobimetinib combination.”

Although objective response rates (ORRs) were found to be similar between the arms, the median duration of response (DOR) was prolonged with the triplet at 21.0 months (95% CI, 15.1 to not evaluable [NE]) versus 12.6 months with vemurafenib/cobimetinib (95% CI, 10.5-16.6).

Patients with BRAF-mutant melanoma typically experience high ORRs with BRAF-plus-MEK combinations, however responses are short-lived in most patients. Immune checkpoint inhibitors are known to provide more durable responses in these patients, but the response rates are relatively lower.5,6

“Collectively, these data lead to the hypothesis that combining BRAF and MEK inhibitors with immune checkpoint inhibition might overcome the clinical limitations of individual classes of therapy, and potentially lead to more durable responses,” explained McArthur.

To this end, investigators launched IMspire150 (NCT02908672), a double-blind, placebo-controlled, multicenter trial. Investigators enrolled patients with previously untreated, advanced BRAF V600-mutant melanoma with ECOG performance scores from 0 to 1, and measurable disease per RECIST v1.1 criteria.

A total of 514 patients were randomized in a 1:1 ratio, stratified by geographic region and centrally tested lactate dehydrogenase (LDH) level (upper limit of normal [ULN] vs >ULN), to receive the BRAF/MEK doublet with either atezolizumab or placebo. Importantly, there was a 28-day run-in with vemurafenib/cobimetinib alone.

Notably, although patients in both arms started vemurafenib at 960 mg twice daily and cobimetinib at 60 mg once daily, the dosing of vemurafenib changed on day 22 in the triplet arm, dropping to 720 mg twice daily. Vemurafenib dosing stayed the same, at 960 mg twice daily, in the doublet arm. From cycle 2 on, either atezolizumab or placebo was given on days 1 and 15 of the 28-day cycle, in addition to vemurafenib/cobimetinib.

The primary end point of the trial was investigator-assessed PFS; key secondary end points included PFS as assessed by an IRC, ORR (confirmed by observations at least 4 weeks apart), DOR, and OS.

“Just over 20 patients who were randomized did not receive their allocated treatment in cycle 2; this leads us to an intent-to-treat population for all the efficacy analyses,” explained McArthur. “For all the safety analyses, patients who did not receive atezolizumab in the triplet-therapy arm were included in the placebo arm for safety analysis.”

Baseline characteristics were similar between arms. In the triplet arm, the median age of patients was 54 years (range, 22-87); 58.6% were male and 94.9% were white. Notably, 79.3% of patients enrolled on the trial were from Europe. Overall, patients enrolled on the trial had good ECOG performance status, with 76.2% at 0 and 23.8% at 1. Importantly, LDH was elevated in approximately 33% of patients in both arms of the study.

Interestingly, at 6 months following randomization, no significant difference in PFS was observed between the arms: 72.8% versus 74.2% in the triplet and doublet arms, respectively. However, by 12 months, 54.0% of patients were free from progression in the atezolizumab arm versus 45.1% of those in the placebo arm. These differences were
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—GRANT A. MCArTHUR, MBBS, PHD

maintained at 18 months and beyond, according to McArthur.

“With respect to outcomes by subgroups, all subgroups favored the atezolizumab arm, including subgroups that looked at patient’s age, LDH levels, and also markers of disease burden and extent of disease by organ site,” noted McArthur.

ORRs were similar between the arms, at 66.3% in the triplet arm versus 65.0% in the doublet arm. In the triplet arm, the ORR was composed of a 15.7% complete response (CR) rate, a 50.6% partial response (PR) rate, and a 22.7% stable disease (SD) rate. In the doublet arm, the CR rate was 17.1%, the PR rate was 48.0%, and the SD rate was 22.8%.

At 12 months, no difference in OS was observed between the arms; however, by 24 months, the OS rate slightly favored the atezolizumab arm at 60.4% versus 53.1% for the placebo arm. The median OS with the triplet was 28.8 months (95% CI, 27.4-NE) versus 25.1 months with the doublet (95% CI, 22.3-NE).

“Ongoing follow-up is critical to determine whether these curves will separate with time,” noted McArthur.

With regard to safety, treatment-related adverse events (AEs) occurred in at least 15% of patients. The rate of treatment-related AEs was similar between the 2 arms; however, pyrexia (37% with triplet vs 25% with doublet), arthralgia (36% vs 26%, respectively), elevated alanine aminotransferase (21% vs 14%), elevated aspartate aminotransferase (22% vs 16%), hyperthyroidism (16% vs 8%), and hypothyroidism (17% vs 6%) were all more common in the atezolizumab arm.

Regardless, these are all expected toxicities for an anti-PD-L1 agent, noted McArthur.

“An important indicator of the overall tolerability of a therapy is the rate of treatment discontinuation because of treatment-related AEs,” said McArthur. “Interestingly, this was very similar between the 2 arms of the trial, being just less than 13% in the atezolizumab arm and just less than 16% in the placebo arm.”

A total of 14 patients—7 in each arm—experienced grade 5 AEs. These events included sepsis (0.9%), septic shock (0.4%), pneumonia (0.4%), hepatic failure (0.4%), hepatitis fulminant (0.4%), and cardiac arrest (0.4%) in the triplet arm. Cardiac arrest, cerebrovascular accident, hydrocephalus, gastrointestinal hemorrhage, and pulmonary hemorrhage were observed in the doublet arm (0.4% each).

Based on these data, the investigators concluded that the triplet combination represents a viable treatment option for patients with BRAF V600–mutant advanced melanoma.

REFERENCES
Investigators Strive to Refine Paradigm for Penile Cancer Treatment

by RACHEL NAROZNIAK, MA

**INVESTIGATORS ARE USING A** novel clinical trial design to test multiple treatment strategies in an effort to define the standard of care in squamous cell carcinoma of the penis, a disease that has been historically difficult to evaluate in prospective, randomized trials due to its rarity.\(^1\,^2\)

The phase 3 International Penile Advanced Cancer Trial (InPACT; NCT02305654), which is enrolling 400 patients with stage T, N1 to N3, M0 squamous cell carcinoma of the penis who have not received prior chemotherapy or chemoradiotherapy, will randomize patients twice to evaluate all combinations of therapy used to date.\(^3\)

The standard modalities used to treat squamous cell carcinoma of the penis include surgery, chemotherapy, and radiotherapy (RT).\(^4\)

Although surgery is rarely sufficient as a singular intervention for patients with inguinal node involvement, how to integrate and sequence chemotherapy and RT to maximize therapeutic benefit in this patient population remains unclear.\(^1\)

Squamous cell carcinoma of the penis is an aggressive cancer that represents 0.4% to 0.6% of all malignant neoplasms in the United States and Europe.\(^2\) The 29% to 40% 5-year survival rate for patients with lymph node (LN)-positive disease and the limited amount of level 1 National Comprehensive Cancer Network (NCCN) evidence to guide treatment decisions translate to a need for clinical investigations that can expand the data available in this space to improve patient outcomes.\(^2\,^4\)

InPACT investigators aim to not only ascertain whether there is a signal for 1 or 2 optimal treatment sequences that lead to improved survival but also standardize them, to ensure that patients with squamous cell penile carcinoma are consistently offered the most effective interventions.

“There are very few men with this disease, and only about 1500 to 2000 men a year will be diagnosed with penile cancer in the United States, [complicating] accrual in clinical trials. For this reason, nobody knows what the correct treatment sequence is and how much is overtreatment and how much is undertreatment,” said Daniel M. Geynisman, MD, an assistant professor in the Department of Hematology/Oncology at Fox Chase Cancer Center, in Philadelphia, Pennsylvania, and a member of the NCCN’s Testicular Cancer Panel.

“This is typically an underserved population, and the goal of this trial is to outline an evidence-based approach for men with lymph node-positive disease,” said Geynisman, who serves as principal investigator of the trial site at Fox Chase Cancer Center.

The primary end point of the InPACT study is overall survival. Secondary end points include disease-specific survival time, the number of patients with grade 3 or grade 4 toxicity, and disease-free survival, among other outcome measures (FIGURE).

**SEARCHING FOR THE OPTIMAL SEQUENCE**

**Randomization 1: InPACT Neoadjuvant**

InPACT’s Bayesian design allows for 2 sequential randomizations: InPACT Neoadjuvant and InPACT Pelvis. During the initial randomization period, patients will be randomized to 1 of 3 treatment arms as investigators assess whether

**FIGURE.** Phase 3 InPACT Trial (NCT02305654)

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<tr>
<th>Eligibility criteria</th>
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<td>Written informed consent</td>
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<td>Histologically confirmed squamous cell carcinoma of the penis N1-3, M0</td>
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<td>Measurable disease by RECIST 1.1 criteria</td>
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<td>ECOG PS of 0-2</td>
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<tr>
<th>Randomization 1: InPACT neoadjuvant (N = 400)</th>
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<tr>
<td>Arm A: No neoadjuvant therapy</td>
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<td>Arm B: TIP</td>
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<td>Arm C: Cisplatin + IMRT</td>
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<th>Pathological assessment: risk for recurrence</th>
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<th>Randomization 2: InPACT pelvis</th>
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<td>Arm P: PLND*</td>
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<td>Arm Q: Surveillance*</td>
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<td>Grade 3/4 toxicities</td>
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<td>Surgical complications</td>
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DFS, disease-free survival; ILND, inguinal lymph node dissection; IMRT, intensity-modulated x-ray therapy; PLND, prophylactic pelvic lymph node dissection; PS, performance status; TIP, paclitaxel, ifosfamide, and cisplatin.

*Patients who have not received neoadjuvant chemotherapy will receive adjuvant chemoradiotherapy. Patients who have had neoadjuvant chemotherapy will have prophylactic PLND alone.

*Patients who have not received neoadjuvant chemotherapy will receive adjuvant IMRT.
neoadjuvant therapy confers a benefit in this patient population. In arm A, patients will undergo standard surgery, inguinal lymph node dissection (ILND), to remove the lymph nodes near the groin where the cancer first presented. Patients in arm B will receive a maximum of 4 cycles of neoadjuvant paclitaxel, ifosfamide, and cisplatin, followed by ILND, and individuals in arm C will be treated with cisplatin and intensity-modulated x-ray therapy (IMRT) prior to ILND.3

The InPACT study’s evaluation of these therapeutic interventions is supported by existing evidence that suggests a benefit with multimodal treatment strategies, including perioperative RT, chemotherapy, and surgery. “The idea is to use systemic chemotherapy first, like we do in a lot of other high-risk cancers such as bladder cancer and breast cancer, to eliminate micrometastatic disease and then go on to surgery,” Geynisman said.

Whereas ILND and lymph node dissection (LNND) are widely recognized as surgical interventions that improve survival outcomes for patients with LN-positive disease, retrospective and prospective data indicate that neoadjuvant cisplatin-based chemotherapy regimens may also confer a survival benefit.4

For example, results reported in 2010 from a phase 2 study (NCT00512096) of neoadjuvant paclitaxel, ifosfamide, and cisplatin and subsequent LND in 30 men with stage 3 or stage 4 squamous cell carcinoma showed that improved time to progression (P < .001) and overall survival (P = .001) were significantly associated with responses to perioperative chemotherapy. Half of the 30 patients who received chemotherapy had an objective response, and at the time of the last clinical assessment, 36.7% of the patients had not experienced disease recurrence.5

Administering chemotherapy in combination with IMRT may afford superior local disease control than neoadjuvant chemotherapy alone, “but it is not clear which approach is better, and for some men, both approaches may actually be overtreatment, which is why there is an arm that only involves inguinal lymph node dissection,” Geynisman said.

Results published in a 2018 study coauthored by Geynisman and Marc C. Smaldone, MD, MSHP, an associate professor in the Department of Surgical Oncology at Fox Chase Cancer Center, showed that only 66.8% of patients with LN-positive disease (750/1123) underwent LN dissection and many did not receive chemotherapy, despite both modalities’ potential to improve patient outcomes.4 In 2013, the NCCN recommended that all patients with LN-positive penile cancer undergo pelvic LND with or without RT and neoadjuvant chemotherapy.

“This trial is so important because a large proportion of patients with penile cancer are not receiving guideline-recommended care,” said Smaldone. “InPACT will help establish appropriate guidelines and make sure that these patients receive the most up-to-date standard of care.”6

**Randomization 2: InPACT Pelvis**

Following stage 1 of the 2-part randomization plan, patients will be stratified based on their risk of recurrence. Only high-risk patients will be eligible for randomization in InPACT Pelvis.3 The objective of this second randomization stage is to determine whether prophylactic pelvic lymph node dissection (PLND) improves survival in patients at a high risk of recurrence following ILND, said Geynisman.

High-risk patients will be randomized to either prophylactic PLND (arm P) or no prophylactic PLND (arm Q). In arm P, patients who did not receive neoadjuvant chemotherapy in part 1 of randomization will be given adjuvant chemotherapy. Patients who received neoadjuvant chemotherapy will undergo prophylactic PLND. Patients randomized to arm Q will undergo surveillance. Individuals assigned to this arm who were not treated with neoadjuvant chemotherapy will be eligible for IMRT.3

Administering adjuvant chemotherapy to individuals who were not given neoadjuvant systemic therapy during the InPACT Neoadjuvant study will help answer the question of whether neoadjuvant chemotherapy is more advantageous than adjuvant chemotherapy.

At present, there is no conclusive evidence that favors one approach over the other.4

**INTERNATIONAL REACH FOR A RARE DISEASE**

Launched in collaboration with Cancer Research United Kingdom/Stand Up To Cancer and the United States National Cancer Institute, the InPACT study is currently enrolling across 17 sites in the United States and United Kingdom.1,3

“This is a one-of-a-kind trial for this disease, and it is really the only trial trying to understand the best treatment for these patients in the world,” said Geynisman, who added that although the trial is actively accruing patients, enrollment is proceeding at a slow pace due to the rarity of squamous cell carcinoma of the penis.

“Usually trials for [uncommon] malignancies are open at large-volume sites, but that is not necessarily where the patients are, [so] it is important for care providers to know that this trial exists and to look for open sites in their area so that their patients can be referred to these places,” Geynisman concluded.

**REFERENCES**


ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

NOW APPROVED

EXTEND HER2+
EXPECTATIONS

After two or more anti-HER2-based regimens for breast cancer in the metastatic setting,

Important Safety Information

Indication
ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

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 a confirmatory trial.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.

- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Please see additional Important Safety Information and a Brief Summary of full Prescribing Information on following pages.

Daiichi-Sankyo | AstraZeneca
ENHERTU monotherapy: durable efficacy

ENHERTU was assessed in a single-arm trial of 184 females with HER2+ unresectable and/or mBC who had received ≥2 prior anti-HER2 therapies. Patients received ENHERTU 5.4 mg/kg IV once every 3 weeks until disease progression or unacceptable toxicity. The major efficacy outcomes were confirmed ORR assessed by ICR using RECIST v1.1 and DOR.1

60.3% ORR

(n=111/184; 95% CI: 52.9, 67.4)b

4.3% CR (n=8) and 56.0% PR (n=103)

14.8 month mDOR

(n=111; 95% CI: 13.8, 16.9)c

Visit ENHERTUhcp.com for more information.

**Important Safety Information (continued)**

**WARNINGS AND PRECAUTIONS**

**Interstitial Lung Disease / Pneumonitis**

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).


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• Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Contraindications
None.

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Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 0.3 to 18.2). Febrile neutropenia was reported in 1.7% of patients. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less. Reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3°C or a sustained temperature of ≥38°C for more than 1 hour), interrupt ENHERTU until resolved. Reduce dose by one level.

Left Ventricular Dysfunction
Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of <40% or absolute decrease from baseline of >20% is confirmed. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within
**Important Safety Information (continued)**

3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure.

**Embryo-Fetal Toxicity**

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

**Adverse Reactions**

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common adverse reactions (frequency ≥20%) were nausea (79%), fatigue (59%), vomiting (47%), alopecia (46%), constipation (35%), decreased appetite (32%), anemia (31%), neutropenia (29%), diarrhea (29%), leukopenia (22%), cough (20%), and thrombocytopenia (20%).

**Use in Specific Populations**

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.

- **Lactation:** There are no data regarding the presence of ENHERTU 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 with ENHERTU and for 7 months after the last dose.

- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.

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

- **Geriatric Use:** Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (53%) as compared to younger patients (42%).

- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see a Brief Summary of full Prescribing Information on following pages.
BRIEF SUMMARY: See package insert for full prescribing information.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Intestinal Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms (see Dosage and Administration (2.2) in the full prescribing information, Warnings and Precautions (5.1)).

- Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception (see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)).

1 INDICATIONS AND USAGE

ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. This indication is approved under accelerated approval based on tumor response rate and duration of response (see Clinical Studies (14.1) in the full prescribing information). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU (see Adverse Reactions (6.1)). In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3). Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., ≥0.5 mg/kg prednisone or equivalent). Withhold ENHERTU until recovery (see Dosage and Administration (2.2) in the full prescribing information). In cases of symptomatic ILD (Grade 2 or greater), promptly initiate corticosteroid treatment (e.g., ≥1 mg/kg prednisone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks). Permanently discontinue ENHERTU in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD (see Dosage and Administration (2.2) in the full prescribing information).

5.2 Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. Median time to first onset was 1.4 months (range: 0.3 to 18.2). Febrile neutropenia was reported in 1.7% of patients. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction (see Dosage and Administration (2.2) in the full prescribing information).

5.3 Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) (see Dosage and Administration (2.2) in the full prescribing information).

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DM1, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Use in Specific Populations (8.1), Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information]. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU (see Use in Specific Populations (8.1, 8.3)).

6 ADVERSE REACTIONS

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

- Intestinal Lung Disease / Pneumonitis [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Left Ventricular Dysfunction [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900). ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31). In the pooled 234 patients, the median age was 56 years (range: 26-96), 74% of patients were ≥65 years, 99.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an ECOG performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, neutropenia, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock. ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (≥2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (≥2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients.

Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU 5.4 mg/kg N=234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>79</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29</td>
</tr>
<tr>
<td>Abdominal paina</td>
<td>19</td>
</tr>
<tr>
<td>Stomatitisb</td>
<td>14</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
</tr>
</tbody>
</table>

General Disorders and Administration Site Conditions

Fatiguec 59 6

Skin and Subcutaneous Tissue Disorders

Alopecia 46 0.4

Rashc 10 0

(continued)
**Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 5.4 mg/kg</th>
<th>ENHERTU 5.4 mg/kg N=234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gough</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>9</td>
<td>2.6k</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and Infestation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>11</td>
<td>0.4n</td>
</tr>
</tbody>
</table>

Events were graded using NCI-CTCAE version 4.03. N=number of patients exposed; PT = preferred term. Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

<table>
<thead>
<tr>
<th>PT</th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Grouped term of fatigue includes PTs of fatigue and asthma.</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>This Grade 3 event was reported by the investigator. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for alopecia is Grade 2.</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>Grouped term of rash includes PTs of rash, rash pustular, rash maculo-papular.</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematoctrit decreased, and red blood cell count decreased.</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>Grouped term of neutropenia includes PTs of neutropenia and neutrophil count decreased.</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>Grouped term of leukopenia includes PTs of leukopenia, lymphopenia, and white blood cell count decreased.</td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Grouped term of thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.</td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>Interstitial lung disease includes events that were adjudicated as IILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, alveolitis.</td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>All events had fatal outcomes (n=6).</td>
<td></td>
</tr>
<tr>
<td>l</td>
<td>Grouped term of headache includes PTs headache, sinus headache, and migraine.</td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>Grouped term of upper respiratory tract infection includes PTs influenza, influenza like illness, upper respiratory tract infection.</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>This Grade 4 event was reported by the investigator. Per NCI-CTCAE v.4.03, the highest NCI-CTCAE grade for dry eye is Grade 3.</td>
<td></td>
</tr>
<tr>
<td>o</td>
<td>Other clinically relevant adverse reactions reported in less than 10% of patients were:</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>- Injury; Poisoning and Procedural Complications: infusion-related reactions (2.6%)</td>
<td></td>
</tr>
<tr>
<td>q</td>
<td>- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 5.4 mg/kg N=234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>70</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>70</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>82</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
</tr>
</tbody>
</table>

(continued)
8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception
Females
ENHERTU can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following 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 ENHERTU and for at least 4 months following the last dose [see Nonclinical Toxicology (13.1) in the full prescribing information].

Infertility
Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility [see Nonclinical Toxicology (13.1) in the full prescribing information].

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

8.5 Geriatric Use
Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (53%) as compared to younger patients (42%).

8.6 Renal Impairment
No dose adjustment of ENHERTU is required in patients with mild ( creatinine clearance (CLcr) ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]. No data are available in patients with severe renal impairment.

8.7 Hepatic Impairment
No dose adjustment of ENHERTU is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see Dosage and Administration (2.2) in the full prescribing information]. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

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

Interstitial Lung Disease
• Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see Warnings and Precautions (5.1)].

Neutropenia
• Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection [see Warnings and Precautions (5.2)].

Left Ventricular Dysfunction
• Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity
• Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)].
• Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months after the last dose [see Use in Specific Populations (8.3)].
• Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose [see Use in Specific Populations (8.3)].

Lactation
• Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see Use in Specific Populations (8.2)].

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

Diagnostics Top List of Priorities in Breast Cancer Research

by RACHEL NAROZNIAK, MA

DEVELOPING DIAGNOSTICS TO IDENTIFY the molecular drivers of breast cancer and model the mechanisms of disease progression will be a key priority of the investigative efforts aimed at improving patient outcomes in the field over the next decade, according to Fabrice André, MD, PhD.

“We need to develop methods to model the biological mechanisms of tumor evolution at the individual level and we need new biotechnology to create new therapies. If we can model the mechanisms of progression, then we can [develop new therapies] to target these mechanisms,” André said during a keynote lecture of the 2020 European Society for Medical Oncology Breast Cancer Virtual Meeting.

Several genomic alterations have already been identified as drivers of disease progression in metastatic breast cancer, such as NFI, KRAS, AKTI, and PIK3R1, which activate intracellular signaling. Drivers in the estrogen receptor pathway include ESR1, which is mutated in approximately 15% of patients, and NCOR1, explained André, director of research at the Institut Gustave Roussy in Villejuif, France.

Epigenetic alterations like KMT2C, which presents in mutant form in about 15% of patients with metastatic disease and promotes resistance to endocrine therapy, represent an “emerging field in breast cancer for which [investigators] are going to generate new drugs,” said André. Understanding whether epigenetic modulation is involved in cancer progression for each patient will be critical to personalizing targeted approaches, he added.

Modeling mechanisms of clonal evolution will be equally important as selecting drivers of disease progression: “We know that metastatic breast cancer can be stable for a long time, and [then], suddenly, the cancer can escape, so we need to understand the mutational processes that [allow escape],” André explained.

APOBEC, a group of cytidine deaminases, and homologous recombination deficiency are 2 genomic scars that could aid not only the genomic evasion of targeted therapy, but also the evolution and aggressiveness of disease.

Biological models of metastatic disease will be needed to determine whether or not these mutational processes are active in patients. The next step in producing biological models involves tracking subclones that can create resistance to therapeutic intervention, and assessing circulating tumor DNA samples at baseline or during patient follow-up may offer an avenue for tracing these subclones, André said. A biologically based modeling methodology will also need to address the molecular mechanisms that promote resistance to immunotherapy, he added.

FOUNDATION FOR BIOTECHNOLOGIES Once investigators are able to identify drivers of disease progression, model mechanisms of clonal evolution and immune escape, and track subclones in each patient with metastatic breast cancer, this knowledge can be used to develop a diagnostic device for target identification that would guide individual treatment decisions. “One of the main priorities in the field of metastatic breast cancer is being able to model the biology [of disease] in each patient in order to propose personalized therapy that specifically targets mechanisms of cancer progression,” André said.

Improving patient outcomes entails a more comprehensive understanding of the biological mechanisms of tumor evolution and the use of new biotechnologies to develop targeted therapies. Biotechnologies could be useful in the development of complex drugs that hit multiple molecular targets, and are already present in breast cancer treatment, where they are used to engineer complex drugs like antibody-drug conjugates and construct the conjugates’ specific or bispecific antibodies. The application of biotechnology in breast cancer drug development has also yielded new linkers that are tailored to the therapeutic need, and cytotoxic agents. As the field advances, André hypothesized that biotechnologies could even be used to develop therapies for individual patients: “My intuition is that, in the future, we could construct a complex drug for each patient based on [their] biology.” Predicting patient outcomes as early as possible in the disease course will also be a priority in the field over the next decade and goes hand in hand with new drug development, André explained. For example, identifying patients with very poor outcomes who are in urgent need of experimental therapies would allow the field to more expeditiously fast-track investigational agents.

DECREASING TOXICITY To move the needle in metastatic breast cancer, the field must prioritize reducing toxicities to subsequently improve quality of life (QOL). “For a very long time, [we have known] that we are using drugs that impact [patients’] quality of life,” André said. “[However], until recently, we did not have evidence based on epidemiology data that the [effects] of systemic treatment are important and relevant for patients.” André cited results from a recent epidemiological study of systemic therapy in pre- and postmenopausal women with early-stage breast cancer. The prospective evaluation of patient-reported outcomes collected from 4262 eligible patients in the CANTO trial (NCT01993498), which studied cancer treatment toxicities in individuals with nonmetastatic breast cancer, “clearly showed that the drugs we are using have a deleterious impact on quality of life,” André said.

Premenopausal women comprised 37.2% of the patient population, and 62.8% of women were postmenopausal. Among premenopausal participants, chemotherapy was found to reduce cognitive functioning. “This is a major need that we need to address,” stated André.

In postmenopausal women, endocrine therapy negatively affected overall health status and QOL score. Interpreting data from the prospective study as a microcosm of the need to reduce the occurrence of adverse events that debilitate QOL, André concluded that “decreasing toxicity to improve [patient] quality of life after cancer is one of the top 4 priorities” in the next decade of breast cancer research.
Heterogeneous Ovarian Cancer Population Needs Innovative Combo Regimens

by GINA COLUMBUS

STRATEGIES WITH PARP INHIBITORS in ovarian cancer should revolve around combining this class of agents with chemotherapy, checkpoint inhibitors, and DNA damage-repair targets to more effectively treat a heterogeneous patient population in the upfront and recurrent settings, explained Susana M. Campos, MD, MPH, in a virtual presentation during the 11th Annual International Symposium on Ovarian Cancer and Other Gynecologic Malignancies.1

"Even though we have trials with different stratifications, eligibility, and designs, we certainly have a heterogeneous patient population," said Campos, an institute physician at Dana-Farber Cancer Institute and assistant professor of medicine at Harvard Medical School in Boston, Massachusetts. "We are starting to see more and more patients with recurrent ovarian cancer, [and] we’re treating them much more aggressively in the upfront setting, and we have to face PARP [inhibitor] resistance in the future. Some of these trials, not only [with] antiangiogenic agents, but [also with] immunotherapy or some of these DNA damage-repair targets, are going to be incredibly important going forward. At the end of the day, what we have to remember is that we craft care to each and every patient.”

In the upfront settings, the use of PARP inhibitors is designed to improve progression-free survival (PFS), objective response rates (ORRs), and overall survival (OS). In the recurrent space, the goal of using this type of therapy is to improve efficacy, overcome resistance, improve immunogenic response, target multiple oncogenic pathways, and provide options for all patients with ovarian cancer, regardless of homologous recombination deficiency (HRD) status, Campos explained.

Nevertheless, the next steps of combining PARP inhibitors with a multitude of other agents, in an effort to improve on these goals, are garnering excitement in the field.

UPFRONT COMBINATIONS

The combination of the PARP inhibitor olaparib (Lynparza) and the angiogenesis inhibitor bevacizumab (Avastin) has been explored in the frontline maintenance setting for patients with advanced ovarian cancer who are in complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy with bevacizumab.

In the double-blind, placebo-controlled, phase 3 PAOLA-1 trial (NCT02477644), patients with newly diagnosed, advanced, FIGO stage III to IV, high-grade, serous or endometroid ovarian, fallopian tube, or peritoneal cancer who had a CR or PR to frontline platinum-based chemotherapy and bevacizumab, regardless of genetic biomarker status or outcome of prior surgery, were randomized 2:1 to receive olaparib combined with bevacizumab (n = 537) or bevacizumab with placebo (n = 269) as a first-line maintenance treatment.

Findings showed that the combination led to a 41% reduction in the risk of disease progression or death compared with bevacizumab alone in this patient population, based on an investigator assessment (HR, 0.59; 95% CI, 0.49-0.72; P < .0001).2 Additionally, after a median follow-up of 22.9 months, the median PFS was 22.1 months and 16.6 months with the combination and bevacizumab alone, respectively. When stratified by somatic BRCA status, the PFS favored the combination in those who were BRCA1 mutant (HR, 0.31; 95% CI, 0.20-0.47) versus those who were not BRCA1 mutant (HR, 0.71; 95% CI, 0.58-0.88).

Results also showed that the benefit with olaparib was most pronounced in patients with tumors positive for HRD, which included tumors with BRCA1 mutations (HR, 0.33; 95% CI, 0.25-0.45). In this subgroup, the median PFS was 37.2 months and 17.7 months with the olaparib combination and bevacizumab alone, respectively.

In those who had HRD-positive tumors without BRCA1 mutations, the median PFS was 28.1 months with olaparib/bevacizumab and 16.6 months with bevacizumab alone, respectively (HR, 0.43; 95% CI, 0.28-0.66). However, with those who had an HRD-negative/unknown status, the median PFS was 16.9 months and 16.0 months with olaparib/bevacizumab and bevacizumab alone, respectively (HR, 0.92; 95% CI, 0.72-1.17).

Based on the PAOLA-1 data, on May 8, 2020, the FDA expanded olaparib’s indication to include the combination for first-line maintenance treatment of adults with advanced...
We are starting to see more and more patients with recurrent ovarian cancer, [and] we’re treating them much more aggressively in the upfront setting...At the end of the day, what we have to remember is that we craft care to each and every patient.”

—SUSANA M. CAMPOS, MD, MPH

epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy with bevacizumab and whose cancer is associated with HRD-positive status, defined by either a deleterious or suspected deleterious BRCA mutation and/or genomic instability (FIGURE).1 Data from other clinical trials may shed light on which patients should receive olaparib plus bevacizumab, Campos said. She mentioned the SOLO-1 trial (NCT01844986) testing olaparib monotherapy and the GOG-218 (NCT00262847) and ICON7 (NCT00483782) trials evaluating bevacizumab plus chemotherapy. “This draws us into the question and question of: What patient population is this combination [in PAOLA-1] most appropriate for? I bring myself back to: ‘Who would I have put bevacizumab on?”

Adding a PARP inhibitor to chemotherapy in patients with high-grade serous ovarian cancer was evaluated in the phase 3 VELIA trial (NCT02470585), which involved the investigational agent veliparib. VELIA randomized patients evenly between 3 arms: the first arm (control) consisted of carboplatin and paclitaxel with placebo followed by placebo maintenance (n = 375). The second arm examined the addition of veliparib to carboplatin/paclitaxel as induction therapy, followed by placebo maintenance (n = 383). In the third arm, veliparib was added at 150 mg twice daily to carboplatin/paclitaxel followed by veliparib alone at 400 mg twice daily as maintenance (n = 382).

Results showed that veliparib plus carboplatin/paclitaxel followed by maintenance veliparib led to a 32% reduction in the risk of progression or death versus placebo/chemotherapy with placebo maintenance in the intent-to-treat (ITT) population.2 The median PFS was 23.5 months compared with 17.3 months in the placebo arm (HR, 0.68; 95% CI, 0.56-0.83; P < .001).

The benefit was more pronounced in those with BRCA mutations. In this group, the median PFS was 34.7 months compared with 22.0 months for veliparib and placebo, respectively (HR, 0.44; 95% CI, 0.28-0.68; P < .001). In a subset of patients with both BRCA mutations and HRD, the median PFS was 31.9 months with the addition of veliparib and 20.5 months for the control arm (HR, 0.57; 95% CI, 0.43-0.76; P < .001).

In patients with BRCA wild-type cancer, the addition of the PARP inhibitor did not demonstrate a PFS benefit versus the control arm, at 18.2 months and 15.1 months, respectively (HR, 0.80; 95% CI, 0.64-0.997). There was a similar effect in patients with BRCA wild-type/HRD (HR, 0.74; 95% CI, 0.52-1.06) and non-HRD (HR, 0.81; 95% CI, 0.60-1.09) disease.

“How do we interpret the VELIA data? It did show a clinically significant improvement of chemotherapy plus the PARP inhibitor followed by the PARP inhibitor,” Campos said. “It draws some questions in terms of the second arm. If you combine chemotherapy with a PARP inhibitor, do you actually just add toxicity, and can you, at that point in time, abbreviate the backbone of that therapy, which is carboplatin/paclitaxel? We have many different patients; [the combinations in PAOLA-1 and VELIA] may have utility in a particular patient group.”

REGIMENS FOR RECURRENT SETTINGS

Combination strategies using PARP inhibition are also being evaluated in the recurrent setting of patients with platinum-sensitive and with platinum-resistant disease. Campos said that although combining PARP with other agents can present challenges, such as dose-limiting toxicities, there are also opportunities to overcome PARP inhibitor-resistance mechanisms and enhance tumor mutational load and immunogenicity.

Some of these studies, which include PARP inhibitors plus antiangiogenic agents, immunotherapy, or chemotherapy, have already reported data showcasing their efficacy, and others are expected to read out in the near future.

For example, olaparib plus the investigational antiangiogenic agent cediranib was explored in a small phase 2 trial (NCT01116648) of 90 patients with platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer, as well as other histologies with deleterious germline BRCA1/2 mutations. Updated findings showed that, in the ITT population, the median PFS was 16.5 months and 8.2 months with the combination and olaparib alone, respectively (HR, 0.50; 95% CI, 0.30-0.83; P = .007).3 The median OS was also improved with the combination, at 44.2 months versus 33.3 months with olaparib alone (HR, 0.64; 95% CI, 0.36-1.11; P = .11).

When stratified by somatic BRCA mutation status, the median PFS was 23.7 months with olaparib/cediranib and 5.7 months with olaparib alone in those who did not harbor somatic BRCA4 mutations (HR, 0.32; 95% CI, 0.16-0.66; P = .002). However, this improvement was not mirrored in the somatic BRCA-mutant carrier subgroup (median PFS, 16.4 and 16.5 months, respectively; HR, 0.75; 95% CI, 0.38-1.49; P = .42).

Similarly, the phase 1/2 AVANOVA study (NCT02354131) investigated the PARP inhibitor niraparib (Zejula) in combination with bevacizumab versus niraparib alone. The regimen was tested in patients with high-grade serous, endometrioid, platinum-sensitive recurrent ovarian cancer who could have received any number of prior therapies. Final survival analysis presented at the American Society of Clinical Oncology 2020 (2020 ASCO) Virtual Scientific Program showed that the median PFS was 12.5 months with niraparib/bevacizumab and 5.5 months with single-agent niraparib (adjusted HR, 0.34; 95% CI, 0.21-0.54; P < .0001).4 Previously reported data demonstrated that the combination improved PFS regardless of HRD (HR, 0.38; 95% CI, 0.20-0.72; P = .0019) or non-HRD status (HR, 0.40; 95% CI, 0.19-0.85; P = .0129).5

“Both of these studies [olaparib/cediranib and AVANOVA] really have paved the way for
CAPMATINIB (TABRECTA) demonstrated high objective response rates (ORRs) that were durable in patients with advanced non-small cell lung cancer (NSCLC) who harbor MET exon 14 skipping mutations, according to findings from cohorts 4 and 5b of the GEOMETRY mono-1 study (NCT02414139) presented during the 2020 American Association for Cancer Research (AACR) Virtual Annual Meeting I.

“The GEOMETRY mono-1 study is in many respects confirmation of a biomarker-identifiable group of patients that benefit from MET inhibition. Capmatinib is an effective agent with a tolerable safety profile that is very appropriate for patients [with MET exon 14 skipping mutations],” said lead study author Edward B. Garon, MD, MS.

The trial grouped patients into 7 cohorts; those in cohort 4 (n = 69) had received at least 1 prior line of therapy, and those in cohort 5b (n = 28) were treatment naïve. The ORR, as per a blinded independent review committee, was 40.6% in cohort 4 and 67.9% in cohort 5b, meeting the primary end point of the trial. The median duration of response (DOR) was 9.72 months and 11.14 months in cohorts 4 and 5b, respectively.

Notably, responses were also observed in patients with central nervous symptom (CNS) involvement (n = 13). These patients were eligible for enrollment if they had stable or asymptomatic brain metastases, despite not having received local therapy. In this population, 7 patients demonstrated a response, including 4 patients with complete resolution of all brain lesions. The other 3 responding patients had complete resolution in 3 lesions with stabilization in 4; complete resolution in 2 lesions with stabilization in 1; and complete resolution in 1 lesion with stabilization in 3, respectively.

In terms of toxicity, 35.6% of patients experienced grade 3/4 adverse events (AEs), the most common of which was peripheral edema (all-grade, 41.6%; grade 3/4, 7.5%). Overall, 21.9% of patients received a dose reduction and 11.1% discontinued therapy due to treatment-related AEs.

Following the presentation of data during the AACR Virtual Annual Meeting I, the FDA granted an accelerated approval to capmatinib for patients with metastatic MET exon14 skipping-mutated NSCLC on May 6, 2020.

In an interview with OncologyLive®, Garon, an associate professor of medicine at the David Geffen School of Medicine, University of California, Los Angeles, discussed the importance of the GEOMETRY mono-1 study and the findings from cohorts 4 and 5b in patients with advanced NSCLC who harbor MET exon 14 skipping mutations.

Could you discuss the unmet need for patients with MET exon 14 skipping mutations?

Patients with MET exon 14 skipping mutations are a recently identified group of patients who appear to have a somewhat worse prognosis overall, certainly compared with some of the patients [who have driver mutation–positive disease treated with] conventional therapies, such as chemotherapy. There are also some emerging data that indicate that perhaps these patients do not do particularly well with immunotherapy either.

What was the design of the trial, and what were some of the key inclusion criteria?

The trial design was somewhat complex. The goal of the trial was to identify the drivers for MET-driven cancers and those who could be effectively treated with capmatinib. Several different cohorts evaluated different lines of treatment, but the focus was on 2 separate populations. One population had potential MET dysregulation based on gene amplification that was determined by the copy number, and the other group had MET exon 14 skipping mutations. The focus of the presentation [during the AACR Virtual Annual Meeting I] was on the group of patients who had MET exon 14 skipping mutations.

What did the results in cohort 4 and 5b show?

Cohort 4 included previously treated patients who had MET exon 14 skipping mutations. Cohort 5b included patients with MET exon 14 skipping mutations who were naïve to prior therapies in the advanced setting. We found that capmatinib was quite active among those patients. The ORR for previously treated patients exceeded 40%, whereas the response rate for treatment-naïve patients was about [66%].

In addition to the ORR, which met its predefined threshold for efficacy in cohorts 4 and 5b, the DOR was good. The DOR was nearly 11 months in patients who had previously received treatment, whereas it was over 11 months in the treatment-naïve cohort.

What AEs were reported with capmatinib?

There were AEs of note. A reasonably large number of patients, as would be imagined, had some AEs. The most common AE was peripheral edema. Most of the AEs were of low grade and only rarely did they lead to treatment discontinuation. There were really no grade 3 or above AEs that led to treatment discontinuation. There were really no grade 3 or above AEs that led to treatment discontinuation in more than 2% of the patient population.

What did the subgroup analysis of patients with brain metastases demonstrate?

One novel aspect of this presentation was the data on patients with brain metastases. Brain metastases are a significant problem among patients with lung cancer, so this is a particularly important topic. There are preclinical data that [show that] capmatinib should have efficacy in the brain. Therefore, as part of the trial design, patients were allowed to enroll, even if they had metastases at the time of enrollment. Patients who hadn’t
received treatment for their brain metastases could also enroll as long as they were clinically asymptomatic.

Fourteen patients had brain metastases at the time of enrollment, and 13 were evaluable for response in the brain. The response was assessed by central review. Disease control was achieved in 12 of those 13 patients. Seven patients had a response. In 4 cases, there was complete eradication of all brain metastases. In other patients, we saw some lesions that were eradicated, whereas others [stabilized or] were reduced in size. [Patients with] brain metastases responded quickly. All of the patients who responded did so by the first analysis. Most of the patients in the brain metastases cohort had not received radiation or other local therapies prior to enrollment.

Could these results impact the timing of molecular sequencing?
That’s going to be an important issue. When we [have FDA-approved therapies for patients with NSCLC who harbor MET exon 14 skipping mutations], we would imagine that laboratories across the world would test for this mutation.

The number of patients in the treatment-naïve cohort was small…29 patients in total, though they did have a particularly impressive ORR and DOR that [were] at least as long as that in previously treated patients. This is a question we are going to want to evaluate more, in larger numbers of patients.

[The results] do underscore the importance of molecular testing. It will be important when one looks at when to test patients. Right now, different centers have different testing paradigms. All centers do try to get a result back for EGFR and ALK within 2 weeks, which is consistent with guidelines from [the International Association for the Study of Lung Cancer] and national or international pathology organizations. This is going to be a question now that we have this very robust frontline data in patients with MET exon 14 skipping mutations.

What are the key messages from the trial?
We now have an identifiable group of patients who have abnormalities in the MET gene, specifically MET exon 14 skipping mutations, where our anticipated outcomes in the previously treated and treatment-naïve settings exceed what we may anticipate from standard therapy. Now, this is not a randomized trial, but the response rates are good.

Is there anything else about the trial you wanted to emphasize?
One strength of the GEOMETRY mono-1 study is that a large number of patients were evaluated, in part because of the design, in which patients with varying levels of gene copy number amplification, as well as patients with MET exon 14 skipping mutations, were included. We have a very large safety database in this group of patients.
Introducing DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION.¹,²*

Approved across 5 indications spanning a wide range of multiple myeloma patients¹

INDICATIONS
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:
• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
• as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
Neutropenia
Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO™ until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO™, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia
Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of platelets.

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO™ can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO™ and for 3 months after the last dose.

The combination of DARZALEX FASPRO™ with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO™. Type and screen patients prior to starting DARZALEX FASPRO™.

Interference with Determination of Complete Response
Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO™-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS
The most common adverse reaction (≥20%) with DARZALEX FASPRO™ monotherapy is: upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common laboratory abnormality (≥40%) with DARZALEX FASPRO™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.

2. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

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Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids [see Dosage and Administration (2.3) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider withholding corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.3) in Full Prescribing Information).

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding daratumumab for Grade 4 neutropenia until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

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Daratumumab may increase thrombocytopenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

**Embry-Fetal Toxicity**

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone recovery of platelets.

**Neonatal depression**

Consider withholding DARZALEX FASPRO until recovery of platelets. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

**Dose interruption**

As defined as dose delays or skipped doses) due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

**Drug interaction**

Dosage interruptions (as defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in ≥5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia. The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
<td>14</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
<td>0</td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
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<td></td>
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<tr>
<td>Insomnia</td>
<td>22</td>
<td>3</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<td></td>
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<tr>
<td>Rash</td>
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<td>0</td>
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<tr>
<td>Pruritus</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>
| **Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.**
| **Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jiroveci pneumonia, pneumonia, and pneumonia bacterial.**
| **Abdominal pain includes abdominal pain, and abdominal pain upper.**
| **Fatigue includes weakness and fatigue.**
| **Edema peripheral includes edema, edema peripheral, and peripheral swelling.**
| **Cough includes cough, and productive cough.**
| **Only grade 3 adverse reactions occurred.**

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) include:

- **General disorders and administration site conditions:** infusion reaction, injection site reaction, chills
- **Infections:** herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** headache, paresthesia
- **Metabolism and nutrition disorders:** hypocalcemia, hyperglycemia
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, pulmonary edema
- **Cardiac disorders:** atrial fibrillation
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone*</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

a Denominator is based on the safety population treated with D-VMP (N=67).

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in ≥5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in >1 patient were pneumonia and anemia.

Table 3 summarizes the adverse reactions in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>43</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spams</td>
<td>31</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>22</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
</tr>
</tbody>
</table>

a Denominator is based on the safety population treated with D-Rd (N=65).

Dosage interruptions due to an adverse reaction occurred in ≥5% of patients included thrombocytopenia.

The most common adverse reaction (=20%) was upper respiratory tract infection.

Table 4 summarizes the adverse reactions in COLUMBA.

Table 4: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>92</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
</tr>
</tbody>
</table>

a Denominator is based on the safety population treated with D-Rd (N=65).

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) include:

• Metabolism and nutrition disorders: decreased appetite
• Cardiovascular disorders: atrial fibrillation
• General disorders and administration site conditions: chills, infusion reaction, injection site reaction
• Vascular disorders: hypertension, hypotension

Table 5 summarizes the adverse reactions in COLUMBA.

Table 5: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24</td>
<td>1%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>15</td>
<td>1%</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>13</td>
<td>2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>5</td>
<td>1%</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>6</td>
<td>1%</td>
</tr>
</tbody>
</table>

a Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.

b Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.

c Fatigue includes asthenia, and fatigue.

d Infusion reactions are those determined by investigators to be related to infusion.

e Cough includes cough, and productive cough.

Clinical relevant adverse reactions in <10% of patients who received DARZALEX FASPRO include:

• General disorders and administration site conditions: injection site reaction, peripheral edema
• Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, muscle spasms
• Gastrointestinal disorders: constipation, vomiting, abdominal pain
• Metabolism and nutrition disorders: decreased appetite, hyperglycemia, hypocalcemia, dehydration
• Psychiatric disorders: insomnia
• Vascular disorders: hypertension, hypotension
• Nervous system disorders: dizziness, partial sensory neuropathy, paresthesia
• Infections: bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B reactivation
• Skin and subcutaneous tissue disorders: pruritus, rash
• Cardiac disorders: atrial fibrillation
• Respiratory, thoracic and mediastinal disorders: pulmonary edema
Daratumumab (daratumumab and hyalurondase-fihj) injection

Table 6: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO Compared to Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>55</td>
<td>43</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>42</td>
<td>39</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

**Immune System**

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 antibodies in the studies described below may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyalurondase products may be misleading.

Treatment-emergent anti-daratumumab antibodies were tested in 451 patients treated with DARZALEX FASPRO as monotherapy or as part of a combination therapy. One patient (0.2%) who received DARZALEX FASPRO as monotherapy tested positive for anti-daratumumab antibodies and transient neutralizing antibodies. However, the incidence of antibody development might not have been reliably determined because the assays that were used have limitations in detecting anti-daratumumab antibodies in the presence of daratumumab. Of the patients who tested positive for anti-daratumumab antibodies, none of the patients who tested positive for anti-hHuPH20 antibodies tested positive for neutralizing antibodies.

**Postmarketing Experience**

The following adverse reactions have been identified with use of intravenous daratumumab. Because these reactions are reported voluntarily from populations of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Hypersensitivity**

- Anaphylactic reaction
- Gastrointestinal: Pancreatitis

**DRUG INTERACTIONS**

**Effects of Daratumumab on Laboratory Tests**

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding. (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

**Fetal/Neonatal Adverse Reactions**

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding. (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

**USE IN SPECIFIC POPULATIONS**

**Embryo-Fetal Toxicity**

- Inform pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, Use in Specific Populations).
- Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm.
- Lenalidomide is only available through a REMS program (see Use in Specific Populations).

**Hepatitis B Virus (HBV) Reactivation**

- Advise patients to inform their healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again (see Warnings and Precautions).
  - Product of Switzerland
  - Manufactured by: Janssen Biotech, Inc.
  - Horsham, PA 19044
  - U.S. License Number 1884
  - © 2020 Janssen Pharmaceutical Companies cp-144555v1
COVID-19 Is Expected to Have Long-term Impact on Oncology Practices

by DENISE MYSHKO

The rapidly developing nature of our knowledge about the coronavirus disease 2019 (COVID-19) and the need to respond quickly to the pandemic are prompting community oncologists to search for ways to maintain their practices while improving the quality of care for their patients.

Oncology practices are spending more on resources while not seeing the volume of patients they once did. Early data indicate that the crisis is having a significant financial impact on community oncology practices, which have reported steep decreases in patient visits, treatments, and new patients.

“We are just beginning to see the tip of the iceberg of the impact on practices and what the financial impact will be,” Jeff Vacirca, MD, chief executive officer of New York Cancer and Blood Specialists (NYCBS), said in an interview with OncologyLive®. “COVID-19 is going to leave a lot of smaller community cancer practices in financial trouble. Oncology practices depend on referrals and referrals depend on surgeries. We have seen elective surgeries now shut down for well over 6 weeks. We’re going to continue to see this impact through the next quarter.”

Medical groups of all sizes and specialties have felt the direct and indirect financial impact of the COVID-19 pandemic, according to a survey of practices that the Medical Group Management Association conducted on April 7 and 8, 2020.1 Although not specific to the oncology field, the survey found on average that practices reported a 55% decrease in revenue and a 60% decrease in patient volume since the beginning of the COVID-19 pandemic. Thirty-six percent of respondents projected there would be layoffs at their practices by May 8 and 60% expected furloughs.1

The impact of the pandemic on oncology practice specifically is widespread, according to a report from HRA®, an analytics company that is part of the MJH Life Sciences™ family of health care services, which includes OncLive®. In an in-depth survey of 51 US oncologists conducted from May 1 to May 11, 73% said they were limiting surgeries to urgent or essential cases and 53% had modified dosing regimens to reduce the need for in-person visits. Additionally, 71% had canceled routine office visits and 14% had cut staff. Among those practices that did make staffing cuts, they furloughed 29% of the staff. On a positive note, 57% of the respondents said they expected their practice to return to pre–COVID-19 levels within 6 to 12 months (FIGURE).

There is a concern that practices that were hanging on are going to be in a tight space, Ted Okon, executive director of the Community Oncology Alliance (COA), said in an interview. “We’re going to see some clinics closing. We’ll see some clinics bought by hospitals. There are some hospitals that are so well endowed…they will have a lot of resources to be able to grab up cancer practices.”

Vacirca says he hopes there is a reset for the cancer care community and hospital systems. “Hospitals systems have learned that they need to be ready for a health care crisis like this and perhaps not concentrate all their time and effort to acquiring practices just for the sake of profit taking.”

FIGURE. HOW ONCOLOGISTS ARE RESPONDING TO PANDEMIC

Actions resulting from pandemic

Your practice is limiting surgeries to urgent or essential cases 73%
Your practice is modifying dosing regimens to reduce the necessity for in-person visits 53%
Your practice is limiting the use of biopsies or other screening methods 51%
Your practice is experiencing delays in molecular testing results 49%
None of the above 12%

Steps taken by practice

Offering telehealth options 76%
CANCELED routine office visits 71%
ONLY offering telehealth service 4%
Furloughed staff 22%
29% of staff furloughed at those practices
Other 4%

When your practice may return to pre-COVID-19 activity level

57% 22% 20% 2%
6-12 months 13 months - 2 years Other

This information was gathered in a survey of 51 oncologists from May 1 to 11 by HRA®, an analytics company that is part of MJH Life Sciences™.
FEDERAL PROGRAMS OFFER FUNDING

In the meantime, practices have been able to take advantage of some federal relief efforts, such as the Paycheck Protection Program or grants from the Department of Health and Human Services (HHS).

Starting in April, the Coronavirus Aid, Relief, and Economic Security Act provided $100 billion to support providers’ health care-related expenses or lost revenue attributable to COVID-19 and to help cover testing and treatment for uninsured Americans. A portion of that funding, $50 billion, was offered as grants to hospitals and providers based on their net patient revenue for 2018. Grants were given in 2 waves, according to a spokesman for HHS. The first wave of $30 billion was based on Medicare fee-for-service reimbursements for 2019. The second wave of $20 billion was calculated so that both grants in total were proportional to providers’ share of 2018 revenue.

Additionally, the Centers for Medicare & Medicaid Services (CMS) in April delivered nearly $34 billion to health care providers through the expansion of the Accelerated and Advance Payment Program. The payments are available to providers who participate in the Hospital Insurance (Part A) and Supplementary Medical Insurance (Part B) programs. The advance payments are separate from the HHS grants and are considered a loan that providers must pay back.

PRACTICE DETAILS PROVIDE A SNAPSHOT

One oncology practice, NYCBS, a multispecialty practice with more than 25 sites across Long Island and New York City, felt the significant impact on care delivery and practice operations due to COVID-19. By the end of March, its weekly average cancellation rate increased by 80%.

NYCBS moved quickly to implement remote visits using telehealth for patients as the pandemic escalated in the greater New York City area. The practice worked with the revenue cycle management team at Flatiron Health to define and track new key performance indicators to report on how remote services were being adopted. Initial results from these efforts indicated a 51.2% acceptance rate for remote visits.

“ar the moment [CMS] gave the go-ahead for remote visits, the Flatiron team along with my team here at NY Cancer had that system up and running within 24 hours,” Vacirca said. “Patients are so grateful that we were able to keep their care continuous throughout this pandemic.

“I believe that remote visits are going to be how we conduct cancer care moving forward,” he added. “It’s not just important for those patients who have a hard time traveling; it’s also important for patients who need second opinions and it’s important for patients who are sick and at home. It makes a huge difference in patient care.”

The team at NYCBS also recognized a need to change their approach to reach even more patients. The practice implemented drive-through services for laboratory and injection services. Additionally, they created a waiting room workflow for in-person appointments that enables patients to check in remotely and wait outside of the clinic until their provider is ready.

After implementing these additional options, the practice saw adoption rates of 70% for drive-through services and 77% for remote waiting rooms. Meanwhile, NYCBS’ cancellation rate decreased and stabilized close to the 2020 weekly average prior to COVID-19.

Although Vacirca said these were important steps to take during the pandemic to ensure patients received care, he would like to get patients back into the office. “Operationally, it works better when people are in the office but at least we know if there is a situation like this again in the future and until this situation ends, we are able to provide the level of care we always have.”

PRACTICE MergERS ARE EXPECTED TO CONTINUE

Although government support and policy changes are helping practices weather the storm, it is unclear if such measures will be enough to stave off consolidation and closures in the future. “It’s perhaps likely, that the painful process of reaching a new health care equilibrium will last well into 2021,” Cutler et al wrote in a recent commentary in JAMA.

Cancer care providers continue to grapple with financial pressures, according to the 2020 Community Oncology Alliance Practice Impact Report. Since 2018, 99 practices have been acquired by hospitals, or have merged with or have been acquired by another community oncology practice or corporate entity, representing a 12% increase. This report was researched before the COVID-19 pandemic, and Okon expects the trend of mergers and acquisitions to continue as community practices deal with the outbreak’s ramifications.

Compiled from public and private data sources, the report provides a look at community oncology trends at the national and state levels over a 12-year period, from January 2008 through April 2020. Since 2008, COA has tracked 435 community oncology practices that have closed, 722 that have been acquired or have become affiliated with hospitals, and 203 that have been merged or acquired by other entities.

The hospital acquisitions, which increased 9.7% from 2008 to 2020, are fueled mostly by financial incentives in the 340B Drug Discount Program and higher payments for cancer care services performed at hospitals, according to COA. Under the 340B program, eligible hospitals are able to obtain drugs at discounted prices and bill private insurers and Medicare at higher rates. Community oncology providers say they cannot compete with the higher margins available to hospitals under the program.

Okon says COA’s report shows that policymakers in Washington are still not doing enough to preserve the independent community oncology system. “At the same time, we are being driven by public policy to deliver higher value and lower costs, all while not enough is being done to stop cancer care from being shifted into the much more expensive hospital setting,” he said in a press release. “The shifting of cancer care to large health systems is the result of the runaway 340B program and disperse site-of-service payments that basically mint money for hospitals.”

NEW WAYS OF WORKING ARE BENEFITING PATIENTS

Cancer care post-COVID-19 will likely look very different from what it did before the pandemic. In fact, social distancing, electronic communications, the implementation of telehealth, and other changes that practices made to their operations to keep their patients and staff safe during this pandemic are likely here to stay.
Mistakes to Avoid When Dealing With a Medical Board Complaint

BY CHRIS MAZZOLINI & LOGAN LUTTON

PHYSICIANS PLAN AND INSURE against the possibility of a medical malpractice suit. However, they often overlook another serious threat to their livelihood: a medical board complaint, which on its own can significantly disrupt your income—and even end a career.

Complaints can result in fines, reputational damage, license suspension, or limitations and even complete license revocation. As a result, it is vital to handle the complaint in an appropriate manner and avoid making crucial mistakes that can cost you.

Here are 9 mistakes to avoid if you are dealing with a medical board complaint.

1. Being uninsured for the costs of medical board complaint defense. These costs can be 6 figures during a time your income may also be disrupted by the complaint.
2. Not being represented by experienced legal counsel in a medical board complaint. Your counsel should be experienced in dealing with your local board’s process, members, and the applicable issues.
3. Failing to inform your insurance carrier about the complaint in a timely manner. This misstep can cause your coverage to be reduced or denied.
4. Not responding to a complaint at all, responding incompletely, or not responding quickly enough to identify qualified counsel and gather evidence required to mount a complete defense.
5. Failing to inform your employer, partners, or organization about the complaint as you may be contractually required to do. This reporting violation can jeopardize your employment or ownership interest, further compounding your problems.
6. Panicking and responding emotionally to the complaint instead of in an organized, tactical way. This type of mistake includes communicating and debating with the complaining patient.
7. Destroying, concealing evidence, or, conversely, talking about the case to third parties, including answering questions or producing evidence without counsel.
8. Making statements or admissions that may be used against you or that may negate your attorney-client privilege with your counsel.
9. Failure to have an asset protection plan in place before the complaint. Acting after your complaint is received to protect your assets from a related medical malpractice lawsuit would almost certainly be considered a fraudulent conveyance/voidable transaction.

For a full list of references, see the article at OncLive.com.
Evidence Supports Value of Physical Activity in Patients With Cancer

by REENA V. JAYANI, MD

PHYSICAL ACTIVITY AND PHYSICAL function are important components of comprehensive care for patients with cancer. Physical inactivity increases the risk of cancer and other chronic health conditions. The United States Department of Health and Human Services has therefore published guidelines on physical activity to mitigate this risk, recommending a cumulative total of 150 to 300 minutes of moderate-intensity physical activity per week. Among those with a sedentary lifestyle, benefit can be seen with even small changes in physical activity. These recommendations are echoed by national guidelines for patients who have cancer and who are receiving cancer-directed therapy, as participation in routine physical activity can improve survival and patient-reported outcomes.

Baseline physical activity and physical function prior to a cancer diagnosis or treatment affects survival, with evidence spanning across solid tumor types and hematologic malignancies. For example, in a national survey of more than 7000 participants, the effect of physical activity in men with prostate cancer was evaluated. Men with a higher level of activity were more likely to be diagnosed with a low-risk tumor, however, this subgroup was also noted to be more likely to have a history of prostate-specific antigen testing. Overall, the benefit of increased physical activity, particularly walking, was associated with a lower risk of prostate cancer-specific mortality.

Likewise, in a phase 3 study evaluating therapies in metastatic colorectal cancer, although no association between vigorous activity and survival was demonstrated, a higher overall survival (OS; 0.9 hours/week vs ≥5.0; HR, 0.80; P = .03) and progression-free survival (HR, 0.78; P = .10) were seen in those who performed at least 5 hours of nonvigorous activity per week. This study also supports the role of physical activity in lessening chemotherapy-related toxicity such as neutropenia (HR, 0.78; P = .04), dehydration (HR, 0.10; P = .002), anorexia (HR, 0.25; P = .03), and fatigue (HR, 0.60; P = .02).

Similar results have been found in patients with blood disorders. In a database study evaluating the role of physical activity in patients with lymphoma, only 46% of patients with lymphoma met the above physical activity recommendations prior to treatment, and these patients experienced significantly higher OS (HR, 0.82; P = .004). Finally, physical function is an alternative method to evaluate physical health and has also been shown to be predictive of survival of those with cancer, particularly in older adults. In a single-institution study of older adults (≥60 years) receiving intensive induction chemotherapy for acute myeloid leukemia, patients with poor physical function before the start of induction had poorer OS (6 vs 16 months; P = .018).

Resilience, an individual’s ability to return to baseline function, is a growing area of research in oncology. Evidence suggests that patients with resilience have improved cancer-related survival. A higher rate of post-diagnosis physical activity in men with prostate cancer has been associated with lower prostate cancer-specific mortality. Among patients with lymphoma, those who met guidelines for physical activity at 3 years after diagnosis had significantly better OS (HR, 0.64; P = .006). This effect of physical activity on OS held true when controlled for disease aggressiveness, comorbidities, and age.

In older adults, resilience may be influenced by underlying medical conditions or physiologic aging. For example, in older adults (≥66 years) receiving inpatient induction chemotherapy for acute myeloid leukemia, a significant decline in physical function was seen in more than 80% of patients at approximately 2 months after discharge. In a study evaluating adjuvant chemotherapy regimens in older women (≥65 years) with breast cancer, nearly 50% of patients were found to be resilient with no decline in physical function. Forty-two percent of women had a decline in function, and of these, 47% recovered to near-baseline physical function. Thirty percent of participants had a decline in physical function at 12 months after chemotherapy initiation. Although promising, these results may represent a more fit population of older adults with cancer, with fewer comorbidities, and higher physical function.

With evidence supporting the role of physical activity and physical function on outcomes of patients with cancer, formal interventions to improve adherence rates of these interventions have been evaluated. In patients with localized breast cancer receiving adjuvant chemotherapy, an exercise intervention of approximately 11 months showed an improvement in patient-reported physical function and quality of life (QOL) from treatment to the completion of the intervention. Of note, there was a compliance rate of 50% to 60%, which is a limiting factor for many exercise interventions. A shorter exercise intervention of 24 weeks in patients with various cancer types and stages receiving chemotherapy had an adherence rate of approximately 70% and showed an improvement in patient-reported physical function and QOL.
In hematologic malignancies, multiple studies have investigated the impact of various exercise interventions. These studies have consistently shown improvement in QOL, physical function, and depression with exercise interventions. Adherence to exercise interventions is a barrier to implementation, and various strategies have been studied to address this limitation, including tailored exercise programs, exercise routines for the patient and their caregiver, and incorporating technology into the exercise intervention.

These studies have demonstrated improved adherence rates and show that the optimal methods of helping patients effectively engage in exercise to improve physical function and QOL are continuously evolving.

The importance of physical activity and physical function is well known in the general population. In patients with cancer, these variables have been shown to have a significant association with patient-reported outcomes and survival. Exercise interventions demonstrate improvements in physical function and QOL, which may also affect an individual's ability to tolerate therapy and alter their treatment course. It is important to encourage patients undergoing active cancer therapy to engage in physical activity and provide support to enable patients where needed.

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“"The importance of physical activity and physical function is well known in the general population. In patients with cancer, these variables have been shown to have a significant association with patient-reported outcomes and survival.”

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A SUBTYPE OF MYELODYSPLASTIC syndromes (MDS) based on the presence of SF3B1 mutations, a nonheritable genetic alteration that causes the disease, represents a clinically distinct population with therapeutic implications, a panel of experts reported in the journal *Blood.*

The mutation, which is found in approximately 1 in 5 patients with MDS, is a biomarker for risk stratification and therapy choices, according to the International Working Group for the Prognosis of Myelodysplastic Syndromes (IWG-PM). The investigators based their findings on an IWG-PM data set of 3479 patients with MDS and a known SF3B1 mutation status from 18 centers or networks. Based on results from the IWG analysis, the following diagnostic criteria for SF3B1-mutant MDS were proposed: cytopenia as defined by standard hematologic values; somatic SF3B1 mutation; isolated erythroid or multilineage dysplasia (with or without ring sideroblasts); bone marrow blasts <5% and peripheral blood blasts <1%; and World Health Organization (WHO) criteria for MDS with isolated del(5q), MDS/myeloproliferative neoplasm with RS and thrombocytosis (MPN-RS-T), or other MDS/MPN, and primary myelofibrosis or other MPN criteria that are not met.

The following genetic lesions represent exclusion criteria for the proposed subtype because of their negative prognostic value and distinct interaction with SF3B1 mutations: poor-risk genetic features, such as monosomy 7 and abnormalities of chromosome 3q26, including inv(3), that lead to gene fusions and EVI1 overexpression, and complex karyotype defined as at least 3 chromosomal abnormalities; and co-occurring RUNX1 and/or EZH2 mutations (FIGURE).

In patients with clonal cytopenia of undetermined significance, the presence of an SF3B1 mutation is linked with subsequent development of overt MDS with RS (MDS-RS), according to the authors of the report. This suggests that the genetic lesion offers presumptive evidence of MDS in the setting of persistent unexplained cytopenia.

Patients with SF3B1-mutant MDS are thought to have a relatively good prognosis and might respond to treatment with luspatercept-aamt (Reblozyl), a drug found to be an effective option for anemia in patients with lower-risk MDS. The agent also eliminates the need for transfusion in some transfusion-dependent patients with MDS-RS.

The FDA approved luspatercept in April 2020 to treat anemia that failed an erythropoiesis-stimulating agent and required at least 2 red blood cell units over 8 weeks in adults who have very low- to intermediate-risk MDS-RS or MDS/MPN-RS-T.

“This study represents an important step forward in the ability to diagnose MDS on the basis of genetic features, and this is paving the way to obtain a diagnosis without the need to analyze bone marrow,” lead investigator Luca Malcovati, MD, of the University of Pavia Medical School in Italy, said in a press release.

**FIGURE. Inclusion and Exclusion Diagnostic Criteria: SF3B1-Mutant MDS**

**Inclusion criteria**
- Cytopenia as defined by standard hematologic values
- Somatic SF3B1 mutation
- Isolated erythroid or multilineage dysplasia (with or without ring sideroblasts)
- Bone marrow blasts <5% and peripheral blood blasts <1%
- WHO criteria for MDS with isolated del(5q), MDS/MPN-RS-T or other MDS/MPN, and primary myelofibrosis or other MPN criteria unmet

**Genetic lesion exclusion criteria**
- Poor-risk genetic features, including monosomy 7
- Abnormalities of chromosome 3q26, leading to aberrant gene fusions and EVI1 overexpression, and complex karyotype defined as ≥3 chromosomal abnormalities
- Co-occurring RUNX1 and/or EZH2 mutations

MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasm; RS-T, ring sideroblasts and thrombocytosis; WHO, World Health Organization.
Ipatasertib (GDC-0068, RG7440): An investigational, ATP-competitive AKT inhibitor\textsuperscript{1,2}

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- No prior systemic therapy for mTNBC

N=1155

**Study Endpoints**

**Primary Outcome Measures:**

- PFS (investigator-assessed), defined as the time from randomization to the first occurrence of disease progression* or death from any cause
- OS, defined as the time from randomization to death from any cause

**Selected Secondary Outcome Measures:**

- ORR, defined as the proportion of patients with a CR or PR on 2 consecutive occasions ≥4 weeks apart*
- DoR, defined as the time from the first occurrence of a documented objective response to disease progression* or death from any cause
- GHS/QoL scores†
- PFS, OS, ORR, and DoR in \textit{PIK3CA}/\textit{AKT1}/\textit{PTEN}-altered tumors

**Selected Eligibility Criteria**

- Histologically documented TNBC that is locally advanced or metastatic and is not amenable to resection with curative intent
- Measurable disease according to RECIST v1.1
- ECOG performance status of 0 or 1
- No prior systemic therapy for inoperable LA/mTNBC
- No history of diabetes requiring insulin

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†As assessed using selected questions from EORTC QLC-C30.

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†As assessed using selected questions from EORTC QLC-C30.
release. “Patients who carry this genetic variant may benefit from treatment with an approved drug, luspatercept. In addition, other potential new treatments that directly target this genetic mutation are in the early stages of development and may benefit patients in the future.”

Patients reported in the data set were originally classified according to the WHO criteria of 2008. These data show that SF3B1 mutations are prevalent in the refractory anemia with RS (RARS) category, accounting for 82% of cases, and the refractory cytopenia with multilineage dysplasia and RS (RCMD-RS) category, accounting for 75% of cases. In addition, SF3B1 mutations were found in 9% of patients with refractory cytopenia with unilineage dysplasia (RCUD) or RCMD.

Investigators found that compared with SF3B1-unmutated MDS, SF3B1-mutated MDS displays significantly lower hemoglobin values, which is consistent with a high degree of ineffective erythropoiesis, higher neutrophil and platelet counts, and lower bone marrow blasts (P < 0.001). Notably, 89% and 86% of patients with SF3B1-mutant MDS had normal or nearly normal neutrophil and platelet counts, respectively, at the time of the registration into the IWG data set.

Of patients with SF3B1-mutated MDS, 44% were women and 56% were men, translating to a male to female ratio of almost 1:1, according to study authors. This profile proves similar to that generally observed with MDS with del(5q), the only genetically defined MDS subtype thus far.

Results from an analysis of the largest cohort of patients with SF3B1-mutated MDS to date demonstrated that the mutation retained an independent positive prognostic value in multivariable analyses, including demographic and disease-related factors, which was confirmed when investigators focused on sideroblastic categories. However, in those with MDS who also had excess blasts, the mutation did not retain a significant impact on survival and risk of disease progression.

These data were confirmed in the IWG data set, in which the SF3B1 mutation identifies a subgroup of patients with MDS with a favorable prognosis (P < 0.001). A stratified analysis of Revised International Prognostic Scoring System (IPSS-R) risk categories for clinical outcomes showed that this positive prognostic value is substantial within categories of very low and low risk; the value is not retained within intermediate- (P = .66) and high- or very high-risk subgroups (P = .11).

Interestingly, the positive prognostic value of the SF3B1 mutation was also confirmed within those with RARS (P < 0.001) and RCMD-RS (P = .003). To estimate the prognostic effect of the mutation in 2016 MDS-RS categories, the investigators created 2 groups of patients: those with RARS and SF3B1-mutated RCUD and those with RCMD-RS and SF3B1-mutated RCMD. When compared with the respective 2016 categories, these groups contained some patients with an SF3B1 mutation and less than 5% of patients with RS. The prognostic value of the mutation was fully confirmed within the category of single-lineage (P < 0.001) and multilineage dysplasia (P = .003), according to the investigators.

“Taken together, these data suggest that within MDS-RS, SF3B1 mutation represents a classification criterion stronger than single-or multilineage dysplasia, and concur to support the recognition of MDS with mutated SF3B1 as a distinct disease entity,” the investigators wrote.

Investigators also noted that in patients with SF3B1-mutated MDS, progression to higher-risk disease or acute myeloid leukemia occurs with a relatively low frequency. With the IWG data set, investigators were able to validate and expand on those observations by evaluating the prognostic value of co-occurring cytogenetic abnormalities and somatic mutations present in the largest group of patients with SF3B1-mutated MDS to date.

Their analysis showed that overall, just 3% of patients with SF3B1-mutated MDS reported in the IWG data set had a poor- or very poor-risk karyotype per IPSS-R stratification. In fact, the percentage was reduced to 1% in patients without excess blasts. Within this subset, a significant effect of IPSS-R poor or very poor cytogenetic risk versus very low-, low-, or intermediate-risk groups was observed on overall survival (OS; P = .032, P = .007, and P = 0.49, respectively). Within those with IPSS-R poor or very poor cytogenetic risk, the negative prognostic value of monosomy 7 was also confirmed (n = 7; P < 0.001).

Moreover, investigators also took a closer look at the relationship between SF3B1 mutation and del(5q) and found that these mutations have been reported in approximately 20% of patients with MDS with isolated del(5q). The co-occurrence of SF3B1 and del(5q) proved consistent with the prevalence of this genotype within the IWG data set. When investigators analyzed the clinical outcome of patients with MDS and isolated del(5q), no significant difference in OS was observed (P = .57). Additionally, the presence or absence of del(5q) did not substantially affect the survival of patients with SF3B1-mutated MDS without excess of blasts (P = .40).

Patients with SF3B1-unmutated MDS-RS appear to be heterogeneous, with a less favorable prognosis and an obscure molecular basis. Additional efforts are needed to clarify the pathophysiology of these disorders, the authors concluded.

REFERENCES
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New Strategies for Targeting CD38 in Multiple Myeloma Take Root

by JANE DE LARTIGUE, PHD

DURING THE PAST 5 YEARS, therapies targeting CD38, a protein highly expressed on the surface of plasma cells, have helped fuel the rapidly growing treatment options for patients with multiple myeloma (MM). Investigators are seeking to build on that success by expanding uses for existing drugs and exploring novel strategies aimed at CD38 activity in MM.

In November 2015, daratumumab (Darzalex) became the first monoclonal antibody (mAb) directed at CD38 to gain FDA approval for patients with MM. The initial indication was for those who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) or are double refractory to those drugs. The uses of daratumumab have since been expanded into various combination regimes in relapsed/refractory and frontline settings.

Daratumumab has now been joined by isatuximab-irfc (Sarcisa), an anti-CD38 mAb with a novel mechanism of action. In March 2020, the FDA approved isatuximab in combination with dexamethasone and the IMiD pomalidomide (Pomalyst) for patients with relapsed/refractory MM who had previously received at least 2 therapies, including a PI and lenalidomide (Revlimid), an IMiD.

Several novel strategies directed at CD38 in MM are in earlier stages of development, including ones utilizing bispecific antibodies and chimeric antigen receptor (CAR) T cells. Notably, BM38, a dual-targeted CAR, recently demonstrated promise in a phase 1 study in relapsed/refractory disease.

MULTIPLE FUNCTIONS OF CD38
Cluster of differentiation 38 is a glycoprotein found on the surface of mature immune cells, with the highest expression levels on the antibody-producing plasma cells. It is also expressed on other lymphoid and myeloid cells, as well as some nonhematopoietic cells.

Originally discovered in the early 1980s as a marker of T-cell differentiation, CD38 has been revealed over the past 4 decades to be a protein with numerous functions. As a receptor for the ligand CD31, CD38 influences cellular processes such as proliferation and adhesion and plays a role in T-cell activation.

CD38 is also now known to have important enzymatic functions, acting as a nicotinamide adenine dinucleotide (NAD)-degrading enzyme (NADase) in several tissues. Specifically, it breaks down NAD into nicotinamide and adenosine diphosphate ribose (ADPR) or, to a lesser extent, cyclic ADPR (cADPR). In this manner, CD38 regulates the homeostasis of NAD, a crucial cofactor in cell signaling and metabolism, while controlling the availability of its metabolites. ADPR acts as a second messenger in calcium signaling and can be further metabolized into the nucleoside adenosine.

In the large majority of cases, CD38 is oriented in the membrane with its catalytic domain outside the cell (type II orientation); thus, it acts as an ectoenzyme, exerting its effects extracellularly. A smaller proportion of CD38 is found on intracellular membranes or on the plasma membrane in a type III orientation, with its catalytic domain facing inside the cell.

Given its primary enzymatic role in the catabolism of extracellular NAD, the fact that the majority of NAD is intracellular seems paradoxical. However, CD38 has also been shown to break down NAD precursors.
before they are taken up into the cell and fed into the NAD biosynthetic pathway. It also is implicated in numerous diseases, including cancer. MM is a plasma cell malignancy, and CD38 has been found to be uniformly highly expressed on MM cells, making it an ideal therapeutic target. Much as in normal cells, studies suggest that CD38 has varied functions in cancer cells, promoting growth, survival, and adhesion. Overall, these mechanisms are conducive to targeting with CD38-directed mAbs (FIGURE). CD38 expression also is thought to contribute to the immunosuppressive microenvironment. It is expressed on many immunosuppressive cell types, including regulatory T and B cells and myeloid-derived suppressor cells. Increased CD38 expression results in increased production of adenosine, which also is immunosuppressive.

DARATUMUMAB SETS THE PACE
Although development of CD38-targeted mAbs in MM began in the 1990s, it was not until 2008 that an agent first entered clinical trials. In 2015, that drug, daratumumab, made history by becoming the first mAb approved for the treatment of MM. Based on results from the phase 1/2 GEN501 (NCT00574288) and phase 2 SIRIUS (NCT01985126) trials, daratumumab was approved as monotherapy for the treatment of patients with relapsed or refractory MM who had received 3 or more prior lines of therapy, including a PI and an IMiD. Because the majority of patients treated with daratumumab ultimately progress, the focus shifted to combinations in an attempt to improve efficacy and response durability. A pair of phase 3 trials, POLLUX (NCT020676009) and CASTOR (NCT02136134), led to the 2016 approval of daratumumab in combination with dexamethasone and either the IMiD lenalidomide or the PI bortezomib (Velcade) in patients with relapsed/refractory MM after at least 1 prior line of therapy. Then, in 2017, results of the EQUULEUS trial (NCT1998971) led the FDA to approve the combination of daratumumab and dexamethasone with a different IMiD, pomalidomide, for the treatment of patients with relapsed/refractory disease after at least 2 prior therapies, including lenalidomide and a PI.

More recently, daratumumab has begun to be evaluated in the frontline setting. The quadruplet regimen of daratumumab, bortezomib, melphalan, and prednisone was evaluated in patients ineligible for autologous stem cell transplant (ASCT) in the phase 3 ALCYONE trial (NCT02195479), leading to FDA approval in 2018. Among 706 patients, the overall response rate (ORR) was 90.9% with the quadruplet regimen and 73.9% without daratumumab. The rates of complete response (CR) and minimal residual disease (MRD) negativity were also significantly higher in the daratumumab arm. The most common grade 3/4 adverse events (AEs) were neutropenia, thrombocytopenia, and anemia. Infusion-related reactions (IRRs) are the most prevalent CD38 mAb-related toxicity, and daratumumab-associated IRRs occurred in 27.7% of patients.

In a recent update, after a median follow-up of 40.1 months, daratumumab was associated with significant improvements in both progression-free survival (PFS; median, 36.4 vs 19.3 months) and overall survival (OS; median not reached; HR for death, 0.60), marking the first report of an OS benefit with daratumumab in patients with MM. In the MAIA trial (NCT02252172), 737 ASCT-ineligible patients with newly diagnosed MM were randomized to receive daratumumab plus lenalidomide and dexamethasone or lenalidomide and dexamethasone alone. Over a median follow-up of 28 months, the ORR was 92.9% versus 81.3% (P < .001), and the median PFS was not reached compared with 31.9 months, respectively. The most common grade 3/4 AEs were neutropenia, lymphopenia, pneumonia, anemia, and leukopenia. IRRs related to daratumumab occurred in 40.9% of patients. On the basis of these results, this combination received approval in 2019.

Also in 2019, daratumumab received its first approval in the frontline setting for patients eligible for ASCT. In the pivotal CASSIOPEIA trial (NCT02541383), 1085 patients received 4 pretransplant induction and 2 posttransplant consolidation cycles of bortezomib, thalidomide, and dexamethasone, with or without daratumumab.

The addition of daratumumab boosted response rates after ASCT; the stringent CR (sCR) rate after consolidation was 29% versus 20% (P = .001), and the percentages of patients achieving CR or better, very good partial response (VGPR) or better, and MRD negativity were also significantly higher. Median PFS was not reached in either group (HR for progression or death, 0.47). The most common grade 3/4 AEs were neutropenia, lymphopenia, and stomatitis.

The ongoing phase 2 GRIFFIN trial (NCT02874742) is evaluating a quadruplet with a different IMiD in this setting (daratumumab plus lenalidomide, bortezomib, and dexamethasone). Data presented at the 2019 American Society for Hematology (ASH) Annual Meeting showed that the sCR rate after consolidation was higher in the daratumumab arm (42.4% vs 32.0%), as were the rates of ORR, CR or better, and VGPR or better. PFS and OS data were immature.

A subcutaneous (SC) formulation of daratumumab has also been developed and was compared with the intravenous (IV) formulation in the phase 3 COLUMBA trial (NCT03277105). Among 552 previously treated patients, the SC formulation demonstrated noninferiority in both primary end points (ORR and pharmacokinetics) and a significantly reduced incidence of IRRs (12.7% vs 34.5%; P < .0001). As a result, the FDA approved the SC formulation of daratumumab in May 2020.

ISATUXIMAB ENTERS THE PICTURE
Isatuximab, the second CD38-targeted mAb approved for the treatment of relapsed/refractory MM, has several distinguishing features. It is a humanized mAb that binds to a different CD38 epitope than daratumumab and has a shorter infusion time compared with daratumumab. Both antibodies have been shown to induce complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity and phagocytosis as part of their antitumor mechanism of action in MM. Isatuximab can also directly induce apoptosis of MM cells without needing to cross-link with Fc- receptors.

Approval was based on the ICARIA-MM trial (NCT02990338), in which the combination of isatuximab, pomalidomide, and dexamethasone significantly improved PFS.
TABLE. Clinical Development of CD38-Targeting Drugs in Select Studies

<table>
<thead>
<tr>
<th>Agent (developer)</th>
<th>Mechanism of action</th>
<th>Tumor type and phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daratumumab (Darzalex) (Janssen Biotech)</td>
<td>Fully human IgG1 CD38 mAb</td>
<td>Phase 3 studies in MRD+ MM, newly diagnosed MM, and high-risk smoldering MM. Phase 2 in R/R Waldenström macroglobulinemia, RR TP53-mutant CLL, R/R AML or high-risk MDS, pediatric ALL, or lymphoblastic lymphoma. Phase 1 in CLL, high-risk localized prostate cancer.</td>
</tr>
<tr>
<td>Isatuximab-irfc (Sarcilisa) (Sanosan-Aventis)</td>
<td>Humanized IgG1 CD38 mAb</td>
<td>Phase 3 in high-risk smoldering MM, MR, MM, newly diagnosed MM. Phase 2 in pediatric hematologic malignancies, RR mCRC, advanced solid tumors.</td>
</tr>
<tr>
<td>TJ202 (I-Mab Biopharma)</td>
<td>Fully human IgG1 CD38 mAb</td>
<td>Phase 2 and 3 in R/R MM.</td>
</tr>
<tr>
<td>GBR 1342 (Glenmark Pharmaceuticals)</td>
<td>Bispecific mAb targeting CD38 and CD3</td>
<td>Phase 1/2 in previously treated MM.</td>
</tr>
<tr>
<td>AMG 424 (Amgen)</td>
<td>Bispecific mAb targeting CD38 and CD3</td>
<td>Phase 1 in R/R MM.</td>
</tr>
<tr>
<td>TAK-573 (Takeda Oncology)</td>
<td>Fully human IgG1 CD38 mAb</td>
<td>Phase 1/2 in R/R MM.</td>
</tr>
<tr>
<td>TAK-169 (Takeda Oncology)</td>
<td>Engineered toxin body; CD38 scFv fused to enzymatically active deimmunized SLTα</td>
<td>Phase 1 in R/R MM.</td>
</tr>
<tr>
<td>CD38 CAR T cells (various companies)</td>
<td>CD38-targeted adoptive cell therapy</td>
<td>Phase 1/2 in R/R AML, R/R MM, R/R B-cell ALL after CD19+ CAR T-cell therapy.</td>
</tr>
<tr>
<td>BM38 (Cellyan Therapeutics)</td>
<td>Dual CD38- and BCMA-targeted adoptive cell therapy (CAR T)</td>
<td>Phase 1/2 in R/R MM.</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; IgG, immunoglobulin G; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; MDS, myelodysplastic syndrome; MM, multiple myeloma; MRD, minimal residual disease; R/R, relapsed or refractory; scFv, single-chain variable fragment; SLTα, Shiga-like toxin A.

*Studies listed on ClinicalTrials.gov.*

compared with pomalidomide and dexamethasone alone (11.5 vs 6.5 months; HR, 0.596; \( P < .001 \)). The most common AEs in the triplet regimen were IRRs, upper respiratory tract infection, diarrhea, bronchitis, and pneumonia. Serious AEs were observed in 62% and 54% of patients, respectively.34

NOVEL STRATEGIES

Beyond daratumumab and isatuximab, several novel CD38-targeting strategies are in development, mostly for MM but also for other hematologic malignancies and for solid tumors, according to a search of the ClinicalTrials.gov website (TABLE).

These include other mAbs such as TJ202 and TAK-079. TJ202, formerly MOR202, was originally developed by MorphoSys in collaboration with Celgene. The companies ended their partnership in 2015, and MorphoSys discontinued development of MOR202 in MM in 2018. However, MorphoSys signed a deal with a Chinese pharmaceutical company, I-Mab Biopharma, which is continuing clinical trials in China and Taiwan (NCT03952091 and NCT03860038).35,36 TAK-079 is a fully human IgG1 mAb that was more effective when administered SC compared with IV infusion in a first-in-human trial in healthy subjects (NCT02219256).37 Results from a phase 1 multicenter study (NCT03499280) in patients with relapsed/refractory MM were presented at ASH 2019. Thirty-one patients had been enrolled across 4 dose cohorts (45, 135, 300, and 600 mg SC). Among 28 patients evaluable for safety, fewer than 1% grade 1 injection-site reactions were reported across more than 500 injections administered. There were no dose-limiting toxicities (DLTs), and the maximum tolerated dose was not reached. Treatment-related AEs (TRAEs) of any grade included fatigue and anemia, and there were 2 grade 3 TRAEs (decreased neutrophil count and anemia). Among 14 patients receiving at least 4 cycles of therapy, the ORR was 43%.38 Takeda is developing 2 other CD38-targeted drugs. TAK-573 is a CD38 mAb fused to attenuated interferon (IFN)-α, which has potent anti-MM activity. TAK-573 acts like an antibody-drug conjugate, targeting delivery of IFN-α to CD38-expressing MM cells to avoid off-target effects. TAK-169 is an engineered toxin body, described as a deimmunized form of the ribosome-inactivating Shiga-like toxin A subunit genetically fused to an antibody fragment that binds to CD38. TAK-169 is designed to internalize into CD38-expressing MM cells and activate ribosomes, directly causing cell death by inhibiting protein synthesis.39-41

Also in development are several bispecific antibodies that bind to both CD38 and the CD3 protein on the surface of T cells, bringing cytotoxic T cells in close proximity to CD38-positive MM cells to facilitate an anti-MM immune response. Glenmark Pharmaceuticals received an orphan drug designation for its GBR 1342 in 2019, and Amgen is developing AMG 424.42,43

CAR T cells are a form of adoptive cell therapy that employs genetically engineered T cells designed to target tumor-specific antigens. CD19-targeted CAR T cells have proved effective in the treatment of several hematologic malignancies and are approved by the FDA. There is considerable interest in generating CAR T-cell therapies targeting alternative antigens, including CD38 and BCMA, as key targets in MM.

Several clinical trials of CD38-targeted CAR T-cell therapies are ongoing. BM38 is being developed by a Chinese company, Cellyan Therapeutics, and is a dual-targeted CAR designed to bind to both CD38 and BCMA. A phase 1/2 study in patients with relapsed/refractory MM is ongoing (NCT03767751), and results from 16 patients treated in the phase 1 dose escalation (0.5, 1, 2, 3, and 4 × 10^6 cells/kg) portion of the trial were presented at ASH 2019.

Median follow-up was 36 weeks, and there were no DLTs. The most concerning toxicities associated with CAR T-cell therapies are cytokine release syndrome (CRS) and neurotoxicity. No grade 3 or higher neurotoxicity occurred, and only 4 patients had grade 3 or higher CRS, which resolved with treatment. ORR was 87.5%, including 8 SCRs, 2 VGPRs, and 4 partial responses. The longest duration of response was more than 51 weeks.3

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Evaluating the Nonmetastatic CRPC Landscape: What Have We Learned?

by CHRISTINA T. LOGUIDICE

Nonmetastatic Castration-Resistant prostate cancer (nmCRPC) is a heterogeneous disease with variable risk of metastasizing. Historically, it has been called M0 CRPC and was a disease entity with great unmet need and little level 1 evidence to guide diagnosis and treatment. However, novel imaging techniques are starting to redefine this disease state, and the FDA approval of 3 androgen receptor (AR)-targeted therapies over the past 3 years is enabling these patients to live free of metastasis longer, with the latest data also showing improved overall survival (OS), when these agents are combined with androgen deprivation therapy (ADT). Although these therapies are well tolerated by most patients, this is a largely asymptomatic group that will require long-term treatment, making it particularly important to avoid untoward treatment-related effects that can compromise their quality of life.

During an OncLive Peer Exchange®, a panel of experts in treating advanced prostate cancer provided their insights on how and when they are using novel imaging versus conventional imaging. They also discussed the data regarding the FDA-approved AR-targeted therapies, how they select between them, and their strategies for mitigating any adverse events (AEs). “It’s been a really exciting time in the world of prostate cancer, particularly advanced prostate cancer, with great breakthroughs,” moderator Neal Shore, MD, said when kicking off the session.

Identifying nmCRPC: PSA Level, Doubling Time, and Novel Imaging

In the 3 pivotal clinical trials that led to the approval of the 3 AR-targeted therapies, patients with nmCRPC were defined as those who experienced a biochemical recurrence (ie, consistently rising prostate-specific antigen [PSA] levels) after having undergone definitive local therapy, whether prostatectomy or radiation, yet had no evidence of metastatic disease on conventional imaging (ie, standard computed tomography [CT] of the abdomen and pelvis and a bone scan). Notably, 2 of the trials enabled patients with greater than 2 cm of measurable disease in their pelvic lymph nodes to enroll. Across the 3 trials, the patients’ PSA doubling time was at least 10 months.

“If [PSA doubling time] is greater than 12 months, we have some data to suggest in biochemical recurrent populations and in nmCRPC populations, that these patients are less likely to die from prostate cancer or develop metastatic disease. So, it really is that patient population with the shorter PSA doubling time, like included in the trials, that I think about treating now that we have data for prolongation of MFS [metastasis-free survival],” panelist Alicia K. Morgans, MD, MPH, said.

The panelists proceeded to discuss how they calculate PSA doubling time and when they pull the trigger to start treating patients. Morgans said she uses an online calculator by Memorial Sloan Kettering, whereas other physicians said they perform the calculation by hand. The panelists indicted there is no clear consensus on when to start treatment based on PSA level and doubling time. “There are some groups who don’t start on ADT until a patient’s...
PSA is 5 to 10 ng/mL and moving rapidly with a short doubling time, whereas others will start right away,” panelist Pedro C. Barata, MD, MSc, said.

Another challenge Barata noted is that the advent of novel imaging modalities, including fluciclovine (Axumin) and gallium-68 prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans, have revealed that many patients with nmCRPC actually have some metastatic disease that cannot be identified using conventional imaging. “If you look at the data in terms of sensitivity, you will know that if you’re going to use fluciclovine—which is FDA approved here in the United States—once you have a PSA greater than 2 ng/mL, your sensitivity or chance of finding metastatic disease is going to be higher, perhaps greater than 50%,” Barata said.

Fluciclovine F18 injection for PET imaging was approved by the FDA in May 2016 to assess prostate cancer status in men with biochemical recurrence. Gallium-68 PSMA is anticipated to be approved soon. “By the end of the summer [2020] we may, in the United States, have ubiquitous access to gallium-68 PSMA imaging. We’re behind the rest of the world, where it’s been around for a long period of time,” Shore said. Nevertheless, many of the panelists have had access to gallium-68 PSMA because of their research activities.

Panelist Nancy Ann Dawson, MD, has been regularly sending some of her patients to the National Institutes of Health for gallium-68 PSMA imaging. She is involved with the ARROW study (NCT03939689), which requires patients to meet certain PSMA-avidity criteria for inclusion. ARROW is investigating the anti-PSMA therapy I-131-1095, a small-molecule radiotherapeutic that selectively binds to the extracellular domain of PSMA, a protein that is highly expressed on prostate cancer cells. Dawson suggested these scans could also be important for patients for whom a prostatectomy is planned. “The data show all the occult disease that’s picked up on PSMA scanning would be pretty important to know,” she said.

As for the fluciclovine scans, Dawson said she does not use them as often as conventional imaging. “The patients I tend to use more of the Axumin [fluciclovine] scans are the patients I don’t find metastases in,” she said. If conventional imaging reveals metastatic disease, Dawson is not necessarily motivated to find more disease by then following up with a novel imaging modality. “The patient is already upset. They have been told they have metastatic disease and they have 3 or 5 lesions. I don’t need to tell them they really have 50 lesions,” she said.

However, if conventional imaging does not show metastatic disease, she may be inclined to use novel imaging to help guide treatment. “If I don’t find anything and I perform an Axumin scan and find a small lymph node up in the patient’s supraclavicular area, my radiation oncologist might want to radiate that oligometastatic disease if the patient does not want to go on hormonal therapy…Mostly, I’m [using these scans to] look for disease that I didn’t already find because I’m planning to do something about it,” she said.

Shore encouraged clinicians to review the 2019 report from the Advanced Prostate Cancer Consensus Conference, which was published April 2020, in European Urology. During the conference, prostate cancer experts from around the world voted on 123 predefined questions regarding areas of controversy across the advanced prostate cancer spectrum, including imaging following biochemical recurrence. The votes strongly favored PSMA PET/CT over any other modalities, gaining 80% of the votes for patients with rising PSA after radiation and 87% of the votes for those with rising PSA after radical prostatectomy. In contrast, fluciclovine or choline PET/CT only received 7% of the vote in the postradiation setting and 4% of the vote in the postprostatectomy setting. “We’re heading into an interesting area, and different working groups are starting to really weigh in on this now and trying to come up with further consensus panels,” Shore said.

It became clear during the discussion that the days of M0 or nmCRPC as a disease entity may be numbered. “When we use conventional imaging, we often can’t see it, [but] some of these newer imaging tests pick up on some metastatic disease in almost all of these patients. This disease state is not only shrinking, but it may go away in the future,” panelist William Oh, MD, surmised.
approved February 2018 based on the SPARTAN trial (NCT01946204); enzalutamide (Xtandi), approved July 2018 based on the PROSPER trial (NCT020032924); and darolutamide (Nubeqa), approved July 2019 based on the ARAMIS trial (NCT02200614). These phase 3 studies were similarly designed and showed a similar MFS survival, which was the primary end point in all 3 trials.2-11

MFS is an unusual end point, and Oh said he was surprised the FDA accepted it, noting it is clinically meaningful. “We know when physical metastases on conventional imaging can be seen—as opposed to fluciclovine or a PSMA—those patients can develop symptomatic disease within a short period of time,” he explained.

Morgans emphasized that she makes her treatment decisions regarding nmCRPC based on conventional imaging findings because this is how the SPARTAN, PROSPER, and ARAMIS trials were designed. “Even if a patient has M1 disease by molecular imaging, as you mentioned, I still feel that patient can benefit from [these] drugs,” she said, noting they are approved across the prostate cancer spectrum, including nmCRPC, metastatic castration-sensitive prostate cancer, and metastatic CRPC. “[Because] there’s benefit across the spectrum, I feel pretty comfortable with that decision,” she said (TABLE 1).12-14

When selecting between apalutamide, enzalutamide, and darolutamide, Morgans said the first thing she considers is their AE profile (TABLE 2).12-14 “They all have their distinct adverse events,” she explained. “Fatigue and hypertension might be more common in enzalutamide; a rash and thyroid problems, as well as some fatigue, may be more common with apalutamide; and darolutamide may still cause a little fatigue. There may be falls across the board, but less so with darolutamide,” she said.

The panelists said other important considerations include patient comorbidities and drug-to-drug interactions, including with other prostate cancer treatments like ADT. “We know that when we put [some] patients on ADT, they complain about tiredness, how they can’t remember where they put their keys, and things that we may not appreciate might be interfering with their lives. There’s a small subset who are really affected cognitively…[and] you’re now adding drugs like enzalutamide, apalutamide, or darolutamide in asymptomatic patients and committing them to years of therapy,” Oh said. Subsequently, he said it is important for clinicians to pay close attention to the AEs their patients are experiencing while on these therapies.

Because patients may not be forthcoming about their AEs, the panelists recommended asking patients and/or their caregivers more detailed questions, such as where they got a bruise/injury, how they are feeling and getting around, and what their day looks like. Oh recounted the case of a patient who came in with a large bruise on his face a few months after starting enzalutamide. After asking the patient about his injury, he learned that the patient had tripped several times while on treatment but did not attribute this to ADT or enzalutamide. Subsequently, if the patient had not presented with the bruise and Oh had not questioned him about it, this AE likely would have been missed.

Another important strategy to identify AEs is to inform patients upfront that multiple drugs are available, so they know they have other options, recommended Dawson. “[Some patients] don’t want to tell me about AEs because they don’t think they have any other

### TABLE 1. Final Primary Outcomes of the SPARTAN, PROSPER, and ARAMIS Trials2-11

<table>
<thead>
<tr>
<th>Overview and outcomes</th>
<th>SPARTAN (N = 1207)</th>
<th>PROSPER (N = 1401)</th>
<th>ARAMIS (N = 1509)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms</td>
<td>2:1 randomization: Apalutamide + ADT (n = 806) vs placebo + ADT (n = 401)</td>
<td>2:1 randomization: Enzalutamide + ADT (n = 933) vs placebo + ADT (n = 468)</td>
<td>2:1 randomization: Darolutamide + ADT (n = 955) vs placebo + ADT (n = 554)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>nmCRPC N0/N1</td>
<td>nmCRPC N0</td>
<td>nmCRPC N0/N1</td>
</tr>
<tr>
<td>PSADT ≤10 months</td>
<td>PSA ≥2 ng/mL</td>
<td>PSA ≥2 ng/mL</td>
<td>PSA ≥2 ng/mL</td>
</tr>
<tr>
<td>Median MFS, months</td>
<td>Apalutamide: 40.5 Placebo: 16.2</td>
<td>Enzalutamide: 36.6 Placebo: 14.7</td>
<td>Darolutamide: 40.4 Placebo: 18.4</td>
</tr>
<tr>
<td>HR for metastasis or death, 0.28 (95% CI, 0.23-0.35; P &lt;.001)</td>
<td>HR for metastasis or death, 0.29 (95% CI, 0.24-0.35; P &lt;.001)</td>
<td>HR for metastasis or death in darolutamide group, 0.41 (95% CI, 0.34-0.50; P &lt;.001)</td>
<td></td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

### TABLE 2. Most Common Adverse Events and Warnings/Precautions12-14

<table>
<thead>
<tr>
<th>Agent</th>
<th>Most common adverse events</th>
<th>Warnings/precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apalutamide</td>
<td>≥10% of patients: Arthralgia Decreased appetite Diarrhea Falls Fatigue Fracture Hot flush Hypertension Rash Weight loss</td>
<td>Embryo-fetal toxicity Falls Fractures Ischemic cardiovascular events Seizures</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>≥10% of patients: Arthralgia Asthenia/fatigue Back pain Constipation Decreased appetite Diarrhea Fatigue Hot flush Hypertension Rash</td>
<td>Embryo-fetal toxicity Falls Fractures Ischemic heart disease Posterior reversible encephalopathy syndrome Seizures</td>
</tr>
<tr>
<td>Darolutamide</td>
<td>≥2% of patients: Fatigue Pain in extremity Rash</td>
<td>Embryo-fetal toxicity</td>
</tr>
</tbody>
</table>
option. The say, ‘You put me on this to make me live longer, and I want to live longer. I guess I’ll just have to put up with this’... Once they realize they might have another option, that allows them to feel more comfortable telling me [there’s something wrong and] instead of this drug I’ve given them to save their life, there might be another one they can try instead,” she said.

In the setting of AEs, the panelists generally preferred switching agents instead of dose reductions or interruptions. “When I had fewer choices, the first thing I would do is stop the therapy and then rechallenge at a lower dose. Now, I [tend to] switch some patients from 1 agent to another because sometimes with dose reductions, they may still have some of those AEs,” Oh said.

Oh found darolutamide to be an especially interesting drug in respect to its AE profile because in clinical trials it was comparable with placebo. “If it’s because it doesn’t cross the blood-brain barrier, then that would be very interesting and intriguing for me as a clinician and for my patients,” he said.

Darolutamide has a different chemical structure than apalutamide and enzalutamide, and studies in rodents suggest darolutamide does not penetrate the blood–brain barrier, unlike apalutamide and enzalutamide.15 In a rat study using radiolabeled darolutamide and enzalutamide, darolutamide had a 10-fold lower blood–brain barrier penetration than enzalutamide, (approximately 0.074 vs 0.765), and it was significantly eliminated from almost all organs and tissues 8 hours after administration, whereas enzalutamide remained constant within the body.16 More studies are needed, but this finding may help explain why seizures have not been associated with darolutamide in clinical trials.

An OS Advantage

Although many patients with nmCRPC will ultimately progress, OS data for darolutamide, enzalutamide, and apalutamide have now matured and show a significant survival advantage with these therapies plus ADT versus placebo plus ADT. Final OS analyses for all 3 agents were presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program. Darolutamide reduced the risk of death by 31% compared with placebo (HR, 0.69; 95% CI, 0.53-0.88; P = .003).17 The OS rates at 3 years were 83% and 77%, respectively. It also delayed the time to pain progression, time to first initiation of cytotoxic chemotherapy, and time to first symptomatic skeletal event.

Enzalutamide showed similar results, reducing the risk of death by 27% compared with placebo (HR, 0.73; 95% CI, 0.61-0.89; P = .001), with a median OS of 67.0 months in the enzalutamide arm and 56.3 months in the placebo arm.18 Fewer men in the enzalutamide arm went on to receive antineoplastic therapies (33% [n = 930] vs 65% [n = 465] in the placebo arm). The survival advantage was slightly lower with apalutamide, which reduced the risk of death by 22% compared with placebo (HR, 0.78; 95% CI, 0.64-0.96; P = .0161), with a median OS of 73.9 months compared with 59.9 months with placebo.19 Like the other AR-targeted therapies, apalutamide reduced the time to cytotoxic chemotherapy.

“It’s quite powerful because drugs like enzalutamide and abiraterone have been around for many years now in the metastatic CRPC setting. Shifting them to earlier use and still having them associated with an OS benefit is a very powerful statement that earlier use of these drugs is really meaningful in terms of OS,” Oh said.

REFERENCES
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1. The Primary Endpoint of Overall PFS was not met in this study
3. bevacizumab (Bevacizumab) allowed at investigator’s discretion, per institutional practice