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PEER EXCHANGE

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Options Multiply in DLBCL

NRG1 Fusions May Be Pan-tumor Target

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CARBONE CANCER CENTER
Stage Is Set for Continued Progress in the Melanoma Clinic
BY MARK R. ALBERTINI, MD

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Bringing the Global Oncology Community Together
ZFJULA is the only once-daily, oral, first-line maintenance monotherapy approved for advanced ovarian cancer in complete or partial response to platinum-based chemotherapy, regardless of biomarker status$^{1-3}$

**Indication**
ZFJULA 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 ZFJULA 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 ZFJULA if MDS/AML is confirmed.

**Hematologic adverse reactions** (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZFJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZFJULA. 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 ZFJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZFJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZFJULA 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 ZFJULA, and refer the patient to a hematologist for further investigations.

**Hypertension and hypertensive crisis** have been reported in patients receiving ZFJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZFJULA 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 ZFJULA. Closely monitor patients with cardiovascular disorders,

Please see additional Important Safety Information on the adjacent page.
If she responds on baseline weight or platelet count, Grade ≥3 administered a starting dose of ZEJULA based 2%, and 2% of patients. In patients who were and neutropenia occurred, respectively, in 4%, 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 have been reported in 15 patients (0.8%) out of 1785 patients received prior chemotherapy with platinum agents from 0.5 months to 4.9 years. These patients had secondary MDS/cancer therapy-related AML varied reported in patients receiving ZEJULA. Discontinuation due to MDS/AML is confirmed.

Important Safety Information

Hematologic adverse reactions (thrombocytopenia, anemia, and neutropenia) have been reported in cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Embryo-Fetal Toxicity and Lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

The most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA included: 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 (56%), increased AST (35%) and increased ALT (29%).

**References:**

**Visit ZEJULA.COM/HCP** to explore the PRIMA data

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NRP/RNA2000037 August 2020
Produced in USA.

Please see Brief Summary on the following pages.
Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 0). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) of full prescribing information).

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

In PRIMA, Grade 4 hypertension occurred in 6% of ZEJULA-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 4 hypertension occurred in 5% of ZEJULA-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRATA, Grade 4 hypertension occurred in 5% of ZEJULA-treated patients with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <2% of patients.

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. Close monitoring of patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension, medically manage/monitor hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).

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

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA (see Use in Specific Populations (8.1, 8.3)).

6 ADVERSE REACTIONS

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

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (see Warnings and Precautions (5.1))
- Bone Marrow Suppression (see Warnings and Precautions (5.2))
- Cardiovascular Effects (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 most common adverse reactions of all grades in >10% of 1,814 patients who received ZEJULA in the pooled PRIMA, NOVA and QUADRATA trials were nausea (65%), thrombocytopenia (63%), anemia (56%), fatigue (55%), constipation (59%), musculoskeletal pain (38%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), diarrhea (13%), urinary tract infection (13%), and hyponatremia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 729 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.3 to 29 months).

Table 1. Adverse Drug Reactions Reported in ≥1% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Grades 1-4%</th>
<th>Grades 3-4%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZEJULA %</td>
<td>Placebo %</td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Anemia</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>General Disorders and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>11</td>
</tr>
<tr>
<td>investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal and Connective</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury*</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, Thoracic and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

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

*CICAE: Common Terminology Criteria for Adverse Events version 4.02 includes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

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

*Includes blood creatine increased, blood area increased, acute kidney injury, renal failure, blood creatinine increased.
### Table 3: Adverse Reactions in ≥50% of Patients Receiving ZELUDA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUDA N=169</td>
<td>Placebo N=86</td>
</tr>
<tr>
<td>ZELUDA N=169</td>
<td>Placebo N=86</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87/66</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74/33</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71/36</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66/57</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66/25</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51/29</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46/21</td>
</tr>
<tr>
<td>Increased creatine</td>
<td>40/23</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>36/34</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35/17</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29/17</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUDA N=169</td>
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</tr>
<tr>
<td>ZELUDA N=169</td>
<td>Placebo N=86</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>81/70</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>70/34</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>63/51</td>
</tr>
<tr>
<td>Increase neutrophils</td>
<td>59/27</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52/30</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>43/17</td>
</tr>
<tr>
<td>Increased creatine</td>
<td>41/22</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>31/19</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29/18</td>
</tr>
</tbody>
</table>

### Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELUDA monotherapy 800 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 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%), the permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZELUDA in these patients was 250 days.

### Table 5: Adverse Reactions in ≥20% of Patients Receiving ZELUDA Based on Baseline Weight or Platelet Count in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUDA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>ZELUDA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85/56</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72/23</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66/37</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>36/23</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>28/15</td>
</tr>
</tbody>
</table>

Table 6: Adverse Reactions in ≥50% of Patients Receiving ZELUDA in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUDA N=367</td>
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<td>85/56</td>
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</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66/37</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>36/23</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>28/15</td>
</tr>
</tbody>
</table>

### Table 7: Adverse Reactions in ≥25% of Patients Receiving ZELUDA Based on Baseline Weight or Platelet Count in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUDA N=367</td>
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</tr>
<tr>
<td>ZELUDA N=367</td>
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</tr>
<tr>
<td>Decrease in hemoglobin</td>
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</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72/23</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66/37</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>36/23</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>28/15</td>
</tr>
</tbody>
</table>

Table 8: Adverse Reactions in ≥20% of Patients Receiving ZELUDA Based on Baseline Weight or Platelet Count in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUDA N=367</td>
<td>Placebo N=179</td>
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<tr>
<td>ZELUDA N=367</td>
<td>Placebo N=179</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85/56</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72/23</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66/37</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>36/23</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>28/15</td>
</tr>
</tbody>
</table>
alkaline phosphatase increased, weight decreased, depression, epistaxis.

Treatment of Advanced Ovarian Cancer After Three or More Chemotherapies

The safety of ZELEA monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 462 patients with recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.01 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range: 0.1 to 30 months).

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

Serious adverse reactions occurred in 43% of patients receiving ZELEA. Serious adverse reactions in >1% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

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

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

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

| Table 7: Adverse Reactions Reported in ≥10% of Patients Receiving ZELEA in QUADRA |
|-----------------------------------------------|---|---|---|
| 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 | |
| | | | |
| Table 8: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELEA in QUADRA |
|-----------------------------------------------|---|---|---|
| Increased hemoglobin | 83 | 26 | |
| Increased glucose | 66 | 5 | |
| Decreased platelets | 60 | 28 | |
| Decreased lymphocytes | 57 | 18 | |
| Increased creatinine | 36 | 4.4 | |
| Increased serum creatinine | 34 | 6 | |
| Increased neutrophils | 42 | 13 | |

6.2 Postmarketing Experience

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

Nervous System Disorders: posterior reversible encephalopathy syndrome (PRES).

Psychiatric Disorders: confusion, delirium, depression, cognitive impairment.

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

Skin and Subcutaneous Tissue Disorders: photosensitivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZELEA can cause fetal harm when administered to pregnant women (see Clinical Pharmacology (12.1) of full prescribing information). There are no data regarding the use of ZELEA in pregnant women to inform the drug-associated risk. ZELEA has the potential to cause teratogenicity and/or embryofetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from ZELEA, advise lactating women not to breastfeed during treatment with ZELEA and for 1 month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Test:

ZELEA can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)).

A pregnancy test is recommended for females of reproductive potential prior to initiating ZELEA treatment.

Contraception

Females

ZELEA 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 ZELEA and for at least 6 months following the last dose.

Infertility

Males

Based on animal studies, ZELEA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (13.1) of full prescribing information).

8.5 Geriatric Use

In PRIMA, 93% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZELEA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mLD (Clcr 60 to 89 mL/min) to moderate (Clcr 30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZELEA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria. The safety of ZELEA in patients with moderate to severe hepatic impairment is unknown.

10 OVERDOSE

There is no specific treatment in the event of ZELEA 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.

17 PATIENT COUNSELING INFORMATION

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

MSD USA

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematologic toxicity or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZELEA (see Warnings and Precautions (5.2)).

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection (see Warnings and Precautions (5.2)).

Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first two months, then 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 (5.5)).

Dosing Instructions

Inform patients on how to take ZELEA (see Dosage and Administration (2.2) of full prescribing information). ZELEA should be taken once daily. Inform patients that if they miss a dose of ZELEA, not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZELEA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy (see Warnings and Precautions (5.2)).

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZELEA and for at least 6 months after receiving the last dose (see Use in Specific Populations (8.3)).

Lactation

Advise patients not to breastfeed while taking ZELEA and for 1 month after the last dose (see Use in Specific Populations (8.3)).

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Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 60.
The chimeric antigen receptor (CAR) T-cell field is bursting with activity, including the potential for new therapies, expanded indications for approved treatments, and earlier use of these medicines in treatment timelines. Experts who help shape the CAR landscape provide their insights in interviews with OncologyLive®.

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CAR Field Shifts Into New Gear

IT HAS BEEN MORE than 6 years since investigators first reported that chimeric antigen receptor (CAR) T-cell therapy led to complete remissions in patients with refractory advanced B-cell lymphomas, a milestone in the development of genetically modified anticancer strategies.¹,²

Today, we are on the verge of a major inflection point in the development of these therapies. There are now 3 FDA-approved CAR T-cell therapies for the treatment of hematologic malignancies, all directed at the CD19 antigen. Two novel agents are in the late stages of review, including a candidate that targets BCMA in multiple myeloma. The next 5 years likely will bring further advancements, potentially in the creation of off-the-shelf allogeneic CAR therapies.

The field is bursting with so much research and innovation that it is difficult to parse out the trends with the greatest potential to affect clinical practice. In this issue of OncologyLive®, we feature insights from some of the investigators who have shaped the CAR landscape from its inception, including Carl H. June, MD, a 2015 Giants of Cancer Care® award winner. One facet of the field today involves its diversity and growth, from studies anchored in a handful of academic institutions to pharmaceutical companies, specialized laboratories, and medical centers.

The number of clinical trials evaluating these approaches provides a measure of the commercial interest in CAR therapies. A recent analysis pegged the number of CAR studies registered on ClinicalTrials.gov at 671, including 357 registered in China and 256 in the United States.³

The volume reflects the enthusiasm for this emerging modality among scientists and investors. We applaud the spirit of innovation that underpins these aspirations and look forward to keeping you up-to-date through our publications and on OncLive.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
BLENREP
belantamab mafodotin-blmf
for injection 100 mg

NOW APPROVED

Please see following pages for Brief Summary of full Prescribing Information, including BOXED WARNING

Learn more today at BLENREPHCP.com
**BLENREP**

(belantamab mafodotin-blmf)

for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

**WARNING: OCULAR TOXICITY**

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

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

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

Perform an ophthalmic exam prior to initiation of BLENREP and during treatment [see Warnings and Precautions (5.1)].

Advise patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist [see Warnings and Precautions (5.1)].

2.2 Recommended Dosage

The recommended dosage of BLENREP is 2.5 mg/kg of actual body weight given as an intravenous infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.

2.3 Dosage Modifications for Adverse Reactions

The recommended dose reduction for adverse reactions is:

- BLENREP 1.9 mg/kg intravenously once every 3 weeks.

Discontinue BLENREP in patients who are unable to tolerate a dose of 1.9 mg/kg (see Tables 1 and 2).

**Corneal Adverse Reactions**

The recommended dosage modifications for corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA), are provided in Table 1 [see Warnings and Precautions (5.1)]. Determine the recommended dosage modification of BLENREP based on the worst finding in the worst affected eye. Worst finding should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity (KVA) scale.

Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale

<table>
<thead>
<tr>
<th>Corneal Adverse Reaction</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td></td>
</tr>
<tr>
<td>Corneal examination finding(s):</td>
<td>Mild superficial keratopathy*</td>
</tr>
<tr>
<td>Change in BCVA:</td>
<td>Decline from baseline of 1 line on Snellen Visual Acuity</td>
</tr>
<tr>
<td></td>
<td>Continue treatment at current dose.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td></td>
</tr>
<tr>
<td>Corneal examination finding(s):</td>
<td>Moderate superficial keratopathy*</td>
</tr>
<tr>
<td>Change in BCVA:</td>
<td>Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200</td>
</tr>
<tr>
<td></td>
<td>Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at same dose.</td>
</tr>
</tbody>
</table>

*Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

b Changes in visual acuity due to treatment-related corneal findings.

Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

*Corneal epithelial defect such as corneal ulcers.

Other Adverse Reactions

The recommended dosage modifications for other adverse reactions are provided in Table 2.

Table 2. Dosage Modifications for Other Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count 25,000 to less than 50,000/mcL</td>
<td>Consider withholding BLENREP and/or reducing the dose of BLENREP.</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>Grade 2 (moderate) or Grade 3 (severe)</td>
<td>Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Grade 3</td>
<td>Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Grade 4</td>
<td>Consider permanent discontinuation of BLENREP if continuing treatment, withhold BLENREP until improvement to Grade 1 or better and resume at reduced dose.</td>
</tr>
</tbody>
</table>

2.4 Preparation and Administration

BLENREP is a hazardous drug. Follow applicable special handling and disposal procedures.1

Calculate the dose (mg), total volume (mL) of solution required, and the number of vials of BLENREP needed based on the patient's actual body weight. More than 1 vial may be needed for a full dose. Do not round down for partial vials.

**Reconstitution**

- Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).
- Reconstitute each 100-mg vial of BLENREP with 2 mL of Sterile Water for Injection, USP, to obtain a final concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. Do not shake.
- If the reconstituted solution is not used immediately, store refrigerated at 36ºF to 46ºF (2ºC to 8ºC) or at room temperature (68ºF to 77ºF [20ºC to 25°C]) for up to 4 hours in the original container. Discard if not diluted within 4 hours. Do not freeze.

(continued on next page)
Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].

5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

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

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)].

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3)]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

(continued on next page)
Relapsed or Refractory Multiple Myeloma

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

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 2.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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

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

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

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

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

Table 3. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

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

6.2 Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells. (see Clinical Pharmacology [12.1], Nonclinical Toxicology [13.1] of full Prescribing Information). Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
From the Editor

HPV Vaccination Is a Battle That Must Be Won

by MAURIE MARKMAN, MD

DESPITE SOLID EVIDENCE that human papillomavirus (HPV) vaccination is remarkably effective in preventing persistent infection by HPV types that are known to be responsible for more than 70% to 80% of cervical cancer cases worldwide, this strategy’s utility in substantially reducing the subsequent development of the malignancy itself remained an open question.¹ Now, the results are in, confirming the major impact of this cancer prevention strategy.

A landmark population-based study in Sweden followed 1,672,983 females aged 10 to 30 years from 2006 to 2017 to evaluate HPV vaccination’s effect on their risk of developing invasive cervical cancer.² As reported in the New England Journal of Medicine, a total of 19 cases of cervical cancer were diagnosed in women who received HPV vaccination (ie, the quadrivalent vaccine) compared with 538 women who were not vaccinated.² The patient population was evaluated for the risk of developing cervical cancer until they were age 31. After adjusting for several relevant covariates, the investigators found that the incidence rate ratio for the development of cervical cancer, comparing women who were vaccinated before age 17 with unvaccinated women, was 0.12. For those aged 17 to 30 years, the incidence rate ratio was 0.47 (TABLE 2). The authors concluded that “among Swedish girls and women 10 to 30 years old, quadrivalent HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level.”³

The scope of this truly remarkable public health outcome probably will become even more impressive with the passage of time. Right now, however, we are at a troubling juncture in our efforts to widely employ a relatively simple and highly cost-effective cancer prevention strategy that has the potential to prevent the immense suffering that can result from advanced cervical malignancies.

To date, societal acceptance of HPV vaccination in the United States has had a difficult history. In the early introduction of strategies to routinely vaccinate adolescent girls in the mid-2000s, there was less than optimal communication with parents. There was an unfortunate focus on the fact that HPV is sexually transmitted rather than on the goal of cancer prevention; specifically, to prevent an infection that over time may lead to several very serious malignancies.

Further, the HPV vaccine strategy quickly caught the attention of those in the growing worldwide antivaccine movement; the potent misinformation campaign began with the infamous publication from Andrew Wakefield that incorrectly linked common childhood vaccinations with autism.³ The disconcerting impact of the growing refusal to vaccinate for potentially deadly infections such as the measles has been painfully documented.⁴

PUBLIC DISTRUST HINDERS UPTAKE

Unfortunately, the turmoil within the federal government’s coronavirus disease 2019 (COVID-19) response has exacerbated concerns regarding public health agencies’ ability to effectively communicate a coherent, believable message regarding the effectiveness and safety of a variety of critically important measures.⁵ In an indication of the magnitude of the distrust of the government’s health-related regulatory environment, the CEOs of 9 pharmaceutical companies working on COVID-19 vaccines felt it necessary to publicly pledge that they would not seek approval of a product unless they felt it had satisfied all necessary requirements for safety and efficacy.⁶

<table>
<thead>
<tr>
<th>TABLE. Key Findings in Swedish HPV Study²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method:</strong> Analysis of cervical cancer risk in 1,672,983 girls and women between the ages of 10 and 30 years from 2006 through 2017</td>
</tr>
<tr>
<td><strong>Cervical cancer cases</strong></td>
</tr>
<tr>
<td>• Unvaccinated: 538</td>
</tr>
<tr>
<td>• Vaccinated: 19</td>
</tr>
<tr>
<td><strong>Incidence rate per 100,000 person-years (95% CI)</strong></td>
</tr>
<tr>
<td>• Unvaccinated: 5.27 (4.84-5.73)</td>
</tr>
<tr>
<td>• Vaccinated: 0.73 (0.47-1.14)</td>
</tr>
<tr>
<td><strong>Adjusted risk ratio (95% CI)</strong></td>
</tr>
<tr>
<td>• Unvaccinated: reference</td>
</tr>
<tr>
<td>• Vaccinated</td>
</tr>
<tr>
<td>◦ Before age 17 years: 0.12 (0.00-0.34)</td>
</tr>
<tr>
<td>◦ From age 17-30 years: 0.47 (0.27-0.75)</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus.
From the Editor

Long before the COVID-19 pandemic generated public health concerns, uptake of the HPV vaccine was falling short. A 2017-2018 survey of parents or caregivers of 82,297 adolescents (aged 13-17 years) showed that 37.1% of eligible individuals were unvaccinated and 10.8% had received just 1 vaccine dose (of a 2- or 3-dose regimen).7 Despite the unequivocal safety and efficacy of HPV vaccination (and all vaccines approved for routine use in the United States8), almost half of this large adolescent population has not received or completed an approach strongly recommended by all major public health agencies to prevent persistent infection with this cancer-causing virus.

According to the survey results, the most common reason parents failed to agree to vaccinate their children involved concerns regarding safety (22.8%), again emphasizing the failure of public health agencies to effectively communicate with large portions of the population.7 Further, the findings indicate that among the adolescents who initiated HPV vaccination but had no intention of completing the series to ensure adequate protection, the major reason (as reported by parents) was the absence of a health care provider’s recommendation to do so (22.2%).

Findings from another study further emphasize concerns related to the lack of physician recommendations for HPV vaccination. In a group of 955 adolescent cancer survivors (aged 9-26 years) who were between 1 and 5 years post completion of anticancer therapy, the patients or their parents reported that 73% of their providers had failed to recommend that they receive this vaccine. This outcome is quite remarkable, considering both the ages of this population and also the fact that young cancer survivors have an increased risk of developing malignancies associated with persistent HPV infections.9

There is a critical need for the overall health care community, including practicing oncologists, to become directly and purposefully involved in effectively communicating, to both patients and their parents, regarding the societal and individual benefits of HPV vaccination as a safe and highly effective approach to cancer prevention.

REFERENCES

**Pembrolizumab Tacks on R/R Classical Hodgkin Lymphoma Indication**

The FDA has approved an expanded label for pembrolizumab (Keytruda) for use as a monotherapy in the treatment of adult patients with relapsed/refractory (R/R) classical Hodgkin lymphoma. Additionally, the agency has approved an update to the pediatric indication for the PD-1 inhibitor’s use, reducing the number of prior lines of therapy from 3 to 2 for pediatric patients with refractory classical Hodgkin lymphoma or classical Hodgkin lymphoma that has relapsed.

Data from KEYNOTE-204 (NCT02684292) demonstrated a 35% reduction in the risk of disease progression or death with pembrolizumab versus brentuximab vedotin (Adcetris; HR, 0.65; 95% CI, 0.48-0.88; P < .0027). Moreover, the median progression-free survival was 13.2 months (95% CI, 10.9-19.4) with pembrolizumab versus 8.3 months (95% CI, 5.7-8.8) with brentuximab vedotin.

**Venetoclax Combo Gets Green Light in Newly Diagnosed AML**

The FDA has granted regular approval to venetoclax (Venclexta) in combination with azacitidine, decitabine, or low-dose cytarabine for patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older or who have comorbidities precluding intensive induction chemotherapy.

The agent received prior accelerated approval for this indication in November 2018. The efficacy of venetoclax was confirmed in 2 randomized, double-blind, placebo-controlled trials in this patient population: VIALE-A (NCT02993523) and VIALE-C (NCT03069352).

Specifically, the median OS was 14.7 months (95% CI, 11.9-18.7) in those who received venetoclax/azacitidine versus 9.6 months (95% CI, 7.4-12.7) in those who were given placebo/azacitidine (HR 0.66; 95% CI, 0.52-0.85; P < .001). Patients who received the venetoclax combination also showed an improvement in complete remission rate versus the placebo, at 37% (95% CI, 31%-43%) versus 18% (95% CI, 12%-25%), respectively.

**FDA Considers Fixed-Dose Schedule for Durvalumab in NSCLC**

The FDA is considering a 4-week fixed dose of durvalumab (Imfinzi) in non–small cell lung cancer (NSCLC) and bladder cancer, where the immunotherapy is already indicated. A formal decision on the supplemental biologics license for the new dosing schedule, which is supported by findings from several studies of durvalumab including data from the pivotal phase 3 CASPIAN trial (NCT03043872), is expected during the fourth quarter of 2020.

If the new dosing option is approved, durvalumab will be administered every 4 weeks at a dose of 1500 mg in individuals with unresectable stage III NSCLC following chemoradiation therapy and in patients with previously treated bladder cancer, consistent with the approved dosing in extensive-stage small cell lung cancer. The proposed, less frequent dosing alternative is additionally expected to minimize the risk of patient exposure to infection in the health care setting. The currently approved durvalumab dosing regimen prescribes weight-based dosing of 10 mg/kg every 2 weeks.

**IMGN632 Receives Breakthrough Designation in R/R BPDCN**

The FDA has granted a breakthrough therapy designation to the CD 123-targeted antibody-drug conjugate IMGN632 for the treatment of patients with relapsed/refractory (R/R) blastic plasmacytoid dendritic cell neoplasm (BPDCN). BPDCN is a rare and aggressive hematologic cancer with features of both leukemia and lymphoma, and it often has lymph node involvement, frequent spread to the bone marrow, and characteristic skin lesions.

Efficacy of the agent was demonstrated in data from the BPDCN cohort of the first-in-human phase 1/2b trial (NCT03386513), in which 2 of 9 patients achieved a complete response with or without complete hematologic recovery. Additionally, 1 patient experienced a partial response. Notably, responses were reported across the patient subsets represented in the overall study population, and in the majority of cases, they occurred following the first or second dose of IMGN632.

Preclinical data have demonstrated the effectiveness of IMGN632 in acute myeloid leukemia, BPDCN, and B-cell acute lymphoblastic leukemia models. Additionally, laboratory studies have shown that the agent results in increased anti-tumor activity when used in combination with other existing therapies that are available for hematologic malignancies.

**Omburtamab Application Is on Hold at FDA for Pediatric Metastatic Neuroblastoma**

The FDA has issued a refuse-to-file letter regarding the biologics license application for the investigational CD276–targeting monoclonal antibody omburtamab for the treatment of pediatric patients with central nervous system/leptomeningeal metastasis from neuroblastoma, according to Y-mAbs Therapeutics, Inc, the developer of the agent.

Following preliminary review of the data submitted for the agent, the regulatory agency determined that certain portions of the chemistry, manufacturing, and control module and the clinical module of the application require further detail. Y-mAbs Therapeutics plans to submit supplementary findings from Study 101 (NCT03275402) focused on tumor response with the agent in the first 24 patients included in the study protocol who are evaluable for disease.

The application was submitted with data from 2 pivotal trials: Study 101 and Study 03-133 (NCT00089245), the latter of which provided the basis for a 2017 breakthrough therapy designation from the FDA.

**Magrolimab Is Expedited for MDS**

The FDA has granted a breakthrough therapy designation to magrolimab for the treatment of patients with newly diagnosed myelodysplastic syndrome (MDS).

In data from an ongoing phase 1b trial (NCT03248479), the first-in-class, investigational anti-CD47 monoclonal antibody in combination with azacitidine was well tolerated and effective for treatment-naïve patients with high-risk and very high-risk MDS. Specifically, the data presented as part of the 2020 European Hematology Association Annual Congress demonstrated that of 33 patients evaluable for efficacy, 91% (n = 30) achieved an objective response to the combination.

 Forty-two percent of patients experienced a complete remission (CR), 24% having a CR in the bone marrow, 3% having a partial remission, and 9% experiencing stable disease. The CR rate in those with 6 months of follow-up or longer was 56%.
Nominate Today!

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

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2021 GIANTS OF CANCER CARE®

PROGRAM OVERVIEW

• Nominations are open through February 2021.
• Domestic and international nominations will be accepted.
• The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
• A selection committee of more than 120 oncologists will vote to determine the 2021 inductees.
• The 2021 Giants of Cancer Care® class will be announced in the spring of 2021.
**Sacituzumab Govitecan Changes Hands in Acquisition**

Gilead Sciences’ acquisition of Immunomedics, the manufacturer of sacituzumab govitecan-hziy (Trodely), is expected to advance the development of the antibody-drug conjugate (ADC) not only across additional types of breast cancer beyond triple-negative disease, but also in other solid tumors.

“The acquirement of Immunomedics will be very meaningful for further development of this agent. With Gilead’s resources, there will be many opportunities to move sacituzumab govitecan into larger studies in earlier disease settings,” said Sara M. Tolaney, MD, MPH, an author on the phase 1/2 IMMU-132-01 trial (NCT01631552) that led to the conditional approval of the ADC, in an interview with OncologyLive®.

Sacituzumab govitecan was approved in April 2020 for patients with third-line metastatic triple-negative breast cancer who have received at least 2 prior therapies for metastatic disease. The agent has shown promise in earlier stages of disease, supporting further study of the Trop-2–directed intervention in more immediate lines of treatment.

“There is so much potential for this agent to be able to move earlier in the metastatic setting and have a bigger role in the early-disease setting, and I think having Gilead develop this agent and move it into these settings is incredible,” said Tolaney.


**Nirogacestat/Teclistamab Combo Is Under Evaluation in Myeloma**

SpringWorks Therapeutics’ investigational gamma secretase inhibitor nirogacestat (PF-03084014) is slated to be evaluated in combination with Janssen Biotech, Inc.’s BCMA- and CD3-targeted bispecific antibody teclistamab (JNJ-64007957) in a phase 1 study in patients with relapsed/refractory multiple myeloma.

The study, which will be sponsored by Janssen, will evaluate the safety, tolerability, and activity of the combination. SpringWorks Therapeutics will assume the costs of manufacturing for nirogacestat and spearhead the creation of a joint oversight committee with Janssen. The study is expected to begin by early 2021, pending regulatory discussions.

In a prior phase 1 study (NCT03145181), teclistamab was found to be safe and effective in patients with relapsed/refractory multiple myeloma. Among patients who had received a median of 6 prior therapies (range, 2-14), 67% experienced an objective response at a dose of 270 µg/kg (n = 12).


**Clinical Collaboration Expands With IDE196/Crizotinib in GNAQ/11+ Solid Tumors**

An ongoing, collaborative clinical trial (NCT03947385) between IDEAYA Biosciences, Inc and Pfizer has been expanded to evaluate the investigational protein kinase C (PKC) inhibitor IDE196 in combination with the multikinase inhibitor crizotinib (Xalkori) for patients with GNAQ- or GNA11-mutated solid tumors, including metastatic uveal melanoma, skin melanoma, lung cancer, and colorectal cancer, according to IDEAYA Biosciences.

The company will sponsor the trial, and Pfizer, which has exclusive worldwide rights to crizotinib, will supply the tyrosine kinase inhibitor. The IDE196/crizotinib arm of the trial is set to be initiated between late 2020 and early 2021. Investigators identified cMET expression or activation as a potential prognostic biomarker of IDE196 treatment in patients with metastatic uveal melanoma. Additionally, they found that the PKC inhibitor demonstrated preclinical synergistic activity with crizotinib in this patient population.

Previously, IDE196 was evaluated as monotherapy in an ongoing, phase 1, dose-escalation basket trial (NCT02601378). Data from the study, which were presented during the 2019 American Association for Cancer Research Annual Meeting, reported an overall response rate of 13% (95% CI, 4%-31%) and a disease control rate of 73% among 30 patients treated with IDE196.

TO READ MORE, VISIT https://bit.ly/31KIqqH.

**DKN-01 Plus Tislelizumab Trial Kicks Off in Gastric/GEJ Cancer**

The first patient has officially been dosed with the investigational anti-Dickkopf-1 antibody (DKN-01) plus tislelizumab (BGB-A317) with or without chemotherapy as part of the ongoing phase 2a DisTinGuish study (NCT04363801) in patients with gastric or gastroesophageal junction (GEJ) cancer. DKN-01 was most recently given a fast track designation by the FDA in September 2020 for the treatment of patients with gastric and GEJ adenocarcinoma with a high-risk of DKK1 tumor expression, as well as those who have progressed following fluoropyrimidine- and platinum-containing chemotherapy, and HER2-targeted therapy.

Previous data showed that in the phase 1/2 P102/KEYNOTE-731 trial (NCT02013154), DKN-01 plus pembrolizumab (Keytruda) demonstrated a median progression-free survival of more than 22 weeks in 10 evaluable patients, and a median overall survival of approximately 32 weeks. Additionally, the overall response rate was 50% and the disease control rate was 80%. In patients with low DKK1 expression, the median progression-free survival was 6 weeks, and the median overall survival and disease control rates were 17 weeks and 20%, respectively.

Physicians & Patients

Now enrolling:
Til Therapy Clinical Trials

Investigational

Explore Til Immunotherapy

Til manufacturing at Iovance starts with isolating tumor-infiltrating lymphocytes (Til) from a surgically resected piece of a patient’s tumor. The isolated Til, which may recognize multiple patient-specific antigens expressed by the tumor, are expanded to billions of cells. Prior to infusion of Til, the patients are treated with non-myeloablative lymphodepletion preconditioning to remove the suppressive tumor micro-environment. Once the Til are infused, the patients receive up to 6 doses of IL-2 to support expansion and anti-tumor activity of the Til.

22 Day Process, One-Time Therapy

You or someone you know may qualify for one of our Til therapy clinical studies if initial criteria are met:

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

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

To learn more about the trials:
Call 1-866-565-4410, and press option 3, email clinical.inquiries@iovance.com or, go to www.iovance.com/clinical/our-clinical-program

Visit clinicaltrials.gov
Cervical Cancer: NCT03108495
Head and Neck Cancer: NCT03083873
Multiple Solid Tumors: NCT03645928
(Melanoma, HNSCC, NSCLC)

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**Drug Spotlight | MITOMYCIN GEL (JELMYTO)**

**First Nonoperative Option Arrives for Low-Grade UTUC**

*by RACHEL NAROZNIAK, MA*

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### A NOVEL COMBINATION OF cytotoxic chemotherapy and the thermal reversible mitomycin gel (Jelmyto) for instillation offers a nonsurgical treatment option for patients with low-grade upper tract urothelial cancer (LG-UTUC), who have historically undergone nephroureterectomy.

On April 15, 2020, the FDA approved mitomycin gel for instillation for adults with LG-UTUC based on complete response (CR) data from the ongoing phase 3 OLYMPUS Study (NCT02793128). Investigators enrolled 71 patients with treatment-naïve or recurrent low-grade, noninvasive UTUC with at least 1 measurable papillary tumor (5 to ≤ 15 mm) located above the ureteropelvic junction. Patients with tumors larger than 15 mm were permitted to have tumor debulking prior to treatment.¹ Fifty-eight percent of patients achieved a CR, and 46% remained in CR at 12 months.²

Mitomycin gel is a mixture of mitomycin in a sterile hydrogel with a temperature-dependent viscosity that allows reconstitution of mitomycin prior to administration and instillation of the cooled mitomycin gel into the upper urinary tract. After administration, mitomycin gel becomes semi-solid at body temperature to form a drug reservoir, which allows for extended exposure of the agent.³

In an interview with *OncologyLive*, Seth P. Lerner, MD, FACS, an author on the OLYMPUS Study and director of Urologic Oncology and the Multidisciplinary Bladder Cancer Program at the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine in Waco, Texas, discussed the complexities of treating LG-UTUC and how mitomycin gel for instillation addresses an unmet need in this space.

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**Q Why is this a difficult patient population to treat, and what makes mitomycin gel novel in this context?**

Mitomycin gel is specifically for patients with low-grade noninvasive cancers of the renal pelvis. With the endoscopic instruments that we have, we can visualize and remove these tumors quite easily, and in many cases, biopsy them. In some cases, we can use laser or electrocautery to eliminate them. The problem is, a good number of these tumors occur in the lower pole part of the renal collecting system, and we cannot get our instruments there.

We see 2 scenarios with these patients: The tumor is not resectable either because of its amount or volume, or because it is located in a part of the kidney that is difficult to access. Oftentimes the only solution is to perform a major operation to remove the kidney.

Mitomycin is a chemotherapy drug mixed with a thermal reversible gel that we would typically use in the kidney for low-grade tumors. However, the chemotherapy drug cannot be retained in the kidney because peristalsis would carry the urine from the kidney into the bladder [and take the drug with it]. The innovation with mitomycin gel was to take a common chemotherapy that urologists have a lot of experience with in the urinary tract and formulate it with a thermo-reversible gel so it stays in the kidney for up to 4 to 6 hours, allowing it to kill any tumors that might be present that we cannot see. Prior to this approval, there was a huge unmet need for these patients who, without any approved therapy, often would have to have their kidney removed.

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**Q Please describe the role the design of OLYMPUS played in tracking the efficacy of mitomycin gel.**

This trial used chemoablation, which entails leaving a tumor in place to measure the effect of the chemotherapy. This was a very clever design because in a single-arm trial, you need to know that there is a tumor in place; that way, when you go back 6 weeks later to evaluate if the tumor is gone, if it is, you know that can only be because the chemotherapy was effective.

At the first disease evaluation, which was 6 weeks after the completion of 6 weekly installations, if the success rate was in the range of 15% to 20%, it would have been acceptable per the standard set by the FDA. We far exceeded those expectations: 59% of patients had no residual tumor at the first disease evaluation.

**Q What adverse events should health care providers be aware of?**

This patient population gets relatively frequent instrumentation of the urinary tract and despite use of internal stents, they are going to be at a higher risk of ureteric stenosis, which was the main significant adverse event observed in the OLYMPUS trial.

The chemotherapy drug is going to cause some inflammation, so inflammation on top of the instrumentation may have contributed to an increased risk of ureteric stenosis. However, the vast majority of these events were manageable with standard techniques that most urologists are comfortable with. For example, some of the investigators gave a short course of steroids. Due to serious stricture disease that could not be managed otherwise, some patients had to have their kidney removed. These events will be part of the informed consent process when we are treating patients.

**Q How does mitomycin gel enact its anticancer activity?**

Mitomycin is an alkylating agent that has a direct cytotoxic effect on tumors. It gets absorbed into the lining of the urinary tract, where it has the opportunity to kill the nascent cancer cells that are in various stages of carcinogenesis. We treat the entire urothelium. Our intent is to get the urothelium exposed to the chemotherapy, which is retained for several hours up in the kidney pelvis so it can have a direct cell-killing effect on any malignant cells that may not be visible by ureteroscopy.

Mitomycin is a chemotherapy drug that has been around for a long time, and it is a therapy that we have used for a few decades. Until now, it did not have an FDA-approved indication for either bladder or upper tract cancer.

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**REFERENCES**


FDA approval—April 15, 2020
FDA grants approval for the alkylating agent mitomycin gel (Jelmyto) for instillation for adults with low-grade upper tract urothelial cancer (LG-UTUC).

**Mechanism of action:**
- Mitomycin inhibits DNA synthesis into RNA.
- The guanine and cytosine content of DNA correlates with the degree of mitomycin-induced cross-linking, and, at high concentrations, mitomycin suppresses cellular RNA and protein synthesis.

**How supplied:**
- Two 40-mg single-dose vials of lyophilized powder of mitomycin for pyelocaliceal solution
- One single-dose vial of 20 mL of sterile, clear gel to be used for reconstitution

**Dosing:**
- Mitomycin instilled 4 mg/mL via ureteral catheter or a nephrostomy tube, with total instillation volume based on volumetric measurements using pyelography.
- Dose not to exceed 15 mL (mitomycin 60 mg).
- Instill once weekly for 6 weeks. Mitomycin may be administered once a month for a maximum of 11 additional instillations in patients with a complete response 3 months after treatment initiation.

**Company:** UroGen Pharma

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**PIVOTAL CLINICAL TRIAL**

The OLYMPUS Study (NCT02793128) is an ongoing, single-arm trial that enrolled 71 patients with treatment-naïve or recurrent noninvasive LG-UTUC with at least 1 measurable papillary tumor (5 mm to ≤ 15 mm) located above the ureteropelvic junction. Patients with larger tumors were permitted to undergo tumor debulking prior to treatment but were required to have 1 remaining visible tumor with a diameter of at least 5 mm.

**BASELINE PATIENT CHARACTERISTICS:**

**Efficacy Population: N = 71**

- **Median age, years (range):** 71 (42-87)
- **Patients with 1 kidney at baseline:**
- **ECOG performance status (%):**
  - 0-1: 10%
  - 2: 90%

- **Patients who underwent tumor debulking before enrollment (%):** 37%
- **Patients with tumors in regions not amenable to endoscopic resection (%):** 63%

**Lesion characteristics (range):**

- **Median diameter of the largest lesion: 10 mm (5-25)**
- **Median total visible tumor burden: 8 mm (5-15)**

**REFERENCES**


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**Efficacy Results in the Olympus Study**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mitomycin (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR* (95% CI)</td>
<td>58% (45%-69%)</td>
</tr>
<tr>
<td><strong>Duration of response</strong> (n = 41)</td>
<td></td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>NR (0-18.8 +)</td>
</tr>
<tr>
<td>CR at 12-month visit*</td>
<td>46%</td>
</tr>
</tbody>
</table>

*Defined as complete absence of tumor lesions at 3 months after treatment initiation.
*Assessed at 12 months ± 2 weeks from CR evaluation.

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**WARNINGS AND PRECAUTIONS**

- **Ureteric obstruction:** Ureteric obstruction, including ureteral stenosis and hydronephrosis, can occur in patients receiving mitomycin. Monitor patients for signs of ureteric obstruction and changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue mitomycin based on the severity of obstruction.
- **Bone marrow suppression:** Test platelet count, white blood cell count differential, and hemoglobin prior to each treatment. Withhold therapy for grade 2 thrombocytopenia or neutropenia. Permanently discontinue for grade 3 or greater thrombocytopenia or neutropenia.
- **Embryo-fetal toxicity:** Can cause fetal harm. Advise women of the potential risk to a fetus and recommend use of effective contraception.

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**Contraindications**

- Contraindicated in patients with perforation of the bladder or upper urinary tract.

**Commonly reported adverse events in the Olympus study**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Mitomycin (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All grade</strong></td>
<td><strong>Grade 3/4</strong></td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>58%</td>
</tr>
<tr>
<td>Ureteric stenosis</td>
<td>44%</td>
</tr>
<tr>
<td>Flank pain</td>
<td>39%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>34%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>32%</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>25%</td>
</tr>
<tr>
<td>Nausea</td>
<td>24%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
</tr>
</tbody>
</table>

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**Lesion characteristics (range):**

- **Median diameter of the largest lesion: 8 mm (5-15)**
- **Median total visible tumor burden: 10 mm (5-25)**

---

**Lesion characteristics (range):**

- **Median diameter of the largest lesion: 8 mm (5-15)**
- **Median total visible tumor burden: 10 mm (5-25)**
**INTERVENE WITH JAKAFI® (RUXOLITINIB) AT DIAGNOSIS**

Ruxolitinib (Jakafi) is a Category 2A* treatment option for both symptomatic lower-risk and higher-risk MF – in patients with platelets ≥50 x 10⁹/L.²¹

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.²

Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate risk based on MIPSS-70 (threshold of ≤3 prognostic variable points), and very low, low, or intermediate risk based on MIPSS-70+ (version 2.0; threshold of ≤3 prognostic variable points).²

In patients who are not transplant candidates.

**SIGNIFICANTLY MORE PATIENTS RECEIVING JAKAFI EXPERIENCED IMPROVEMENT IN MF-RELATED SPLENOMEGALY¹,³,⁵**

**COMFORT-I PRIMARY ENDPOINT¹,³²**

<table>
<thead>
<tr>
<th>of patients receiving Jakafi</th>
<th>of patients receiving placebo (P &lt; 0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42% achieved a ≥35% reduction in spleen volume at week 24</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

4.4 years median duration of spleen response among primary responders (n = 65)⁴³

**COMFORT-II PRIMARY ENDPOINT¹,⁵¹**

<table>
<thead>
<tr>
<th>of patients receiving Jakafi</th>
<th>of patients receiving best available therapy¹ (P &lt; 0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29% achieved a ≥35% reduction in spleen volume at week 48</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Indications and Usage**

Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

**Important Safety Information**

- **Treatment with Jakafi (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated**
- **Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary**
- **Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi**
- **Severe neutropenia (ANC <0.5 x 10⁹/L) was generally reversible by withholding Jakafi until recovery**
- **Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines**
- **Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination**
- **Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi. Monitor and treat patients with chronic HBV infection according to clinical guidelines**
- **When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt therapy before consulting a physician**

For more data on long-term results with Jakafi, visit Jakafi Results.com

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ⁱ For adults with intermediate- or high-risk myelofibrosis (MF)¹

² To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their content, use or application in any way.

³ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelofibrosis. All other trademarks are the property of their respective owners.
Managing thrombocytopenia by reducing the dose or temporarily interrupting treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks. Neutropenia, which are each dose-related effects. Perform a clinical guidelines promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

‡ In patients who are not transplant candidates.

For adults with intermediate- or high-risk myelofibrosis (MF)1 who achieve a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI.1,5

A phase 3 study with 219 patients with intermediate-2–risk or high-risk MF. The primary endpoint was the proportion of patients achieving a >35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.1,7

Duration of spleen response was defined as the interval between the first spleen response measurement that was a >35% reduction from baseline and the date of the first measurement that was no longer a >35% reduction from baseline that was also a >25% increase from nadir.

Overall survival was a prespecified secondary endpoint in COMFORT-I1

Overall survival was a prespecified secondary endpoint in COMFORT-II1

JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 51%4

All patients in the placebo group either crossed over to Jakafi at a median of 9 months or discontinued1

The 5-year overall survival analysis is not included in the Full Prescribing Information for Jakafi. Although the 3-year overall survival analysis is presented in the Full Prescribing Information, P-values and hazard ratios are omitted from the overall survival Kaplan-Meier curves.

COMFORT-I was not designed to compare survival probabilities between Jakafi and placebo at 3 or 5 years.4

Patients randomized to placebo were eligible to cross over to receive Jakafi because of progression-driven events or at the physician’s discretion; however, these patients continued to be grouped within their original randomized assignment for analysis purposes.

COMFORT-I (Controlled Myelofibrosis study with ruxolitinib) was a randomized, double-blind, placebo-controlled phase 3 study with 310 patients. The primary endpoint was the proportion of patients achieving a >35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.1,7

B) 3 and 5 years.4

In COMFORT-II, 5-YEAR ANALYSIS OF JAKAFI AND BEST AVAILABLE THERAPY7

At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy7

Overall survival was a prespecified secondary endpoint in COMFORT-II1

JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 56%7

All patients in the best available therapy group either crossed over to Jakafi at a median of 17 months or discontinued1

B) 3 and 5 years.4

In COMFORT-II, 5-YEAR ANALYSIS OF JAKAFI AND PLACEBO6

At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo1

Overall survival was a prespecified secondary endpoint in COMFORT-I1

Overall survival Kaplan-Meier Curves by Treatment Group in COMFORT-I8,6,8,8

Overall survival Kaplan-Meier Curves by Treatment Group in COMFORT-II7,8,8

For more data on long-term effects with Jakafi, visit JakafiResults.com

or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.

Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥5%) were infections.

Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.

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

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

To learn more about Jakafi, visit HCP.Jakafi.com.


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All other trademarks are the property of their respective owners.

Jakafi®
ruxolitinib (Tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE Myelofibrosis: Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. Polycythemia Vera: Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have an inadequate response to or are intolerant of hydroxyurea. Acute Graft-Versus-Host Disease: Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Thrombocytopenia, Anemia and Neutropenia: Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Dosage and Administration (2.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2.1), and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Performed treatment completion blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2.1), and Adverse Reactions (6.1) in Full Prescribing Information].

Risk of Infection Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. Tuberculosis Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate prompt treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. Polycythemia Vera: Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have an inadequate response to or are intolerant of hydroxyurea. Acute Graft-Versus-Host Disease: Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

Non-Melanoma Skin Cancer: Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. Lipid Elevations: Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: •Thrombocytopenia, Anemia and Neutropenia [see Warnings and Precautions (5.1) in Full Prescribing Information]. Risk of infection [see Warnings and Precautions (5.1) in Full Prescribing Information]. •Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see Warnings and Precautions (5.3) in Full Prescribing Information]. •Non-Melanoma Skin Cancer [see Warnings and Precautions (5.4) in Full Prescribing Information].

Clinical Trials Experience in Myelofibrosis: 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 Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 4.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2]. Thrombocytopenia, anemia and neutropenia are dose-related effects.

The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Bruising</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>96</td>
<td>34</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>6</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 3 continued.
**Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 &lt;1 &lt;1</td>
<td>58 0 0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 5 &lt;1 3</td>
<td>24 3 &lt;1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 &lt;1 10</td>
<td>10 0 0</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35 0 0 0</td>
<td>8 0 0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25 &lt;1 0 0</td>
<td>16 0 0</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>23 0 0 0</td>
<td>23 &lt;1 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 0 0 0</td>
<td>13 0 0</td>
</tr>
</tbody>
</table>

*Presented values are worst Grade values regardless of baseline*

| National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

**Clinical Trial Experience in Acute Graft-Versus-Host Disease**

In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for acute GvHD failing treatment with steroids with or without other immunosuppressive drugs [see Clinical Studies (14.3) in Full Prescribing Information]. The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=71)</th>
<th>Best Available Therapy (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Infections</td>
<td>55 41</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>51 13</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>49 20</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 14</td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>32 28</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32 7</td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>31 14</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>25 11</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 7</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>23 3</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 4</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 13</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 0</td>
<td></td>
</tr>
</tbody>
</table>

*Selected laboratory abnormalities are listed in Table 6 below*

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=71)</th>
<th>Best Available Therapy (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>75 45</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75 61</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 40</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>48 8</td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>48 6</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 1</td>
<td></td>
</tr>
</tbody>
</table>

*National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

**Drug Interactions**

Concomitant administration of Jakafi with fluoropyrimidine, methotrexate, and/or its metabolites was present in the milk of lactating rats (2% to 2.5% of the maternal plasma). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose.

**OVERDOSAGE**

There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myeloproliferative neoplasms (Cohort B). Jakafi is a registered trademark of Incyte. All rights reserved.
French Study Sheds Light on COVID-19 Stress Among Patients With Cancer

by RACHEL NAROZNIAK, MA

Patients on active therapy during the coronavirus disease 2019 (COVID-19) pandemic, as well as oncology care providers, have increased levels of perceived and posttraumatic stress, according to preliminary data from the COVIPACT study. These data highlight a gap in psychosocial support resources that help promote emotional resilience and reduce the risk of posttraumatic stress in patients on active therapy.

Baseline results from the prospective trial (NCT04366154) presented at the European Society for Medical Oncology Virtual Annual Congress 2020 showed that “there was a high level of stress among patients,” according to Florence Joly, MD, PhD, who led the data review.

Between April 8 and May 29, 2020, during the French lockdown, investigators collected questionnaire responses on patients’ psychoemotional status. The COVIPACT population included 621 patients with hematological malignancies or solid tumors receiving systemic therapies from the outpatient departments of 2 respective French cancer centers. Assessing the proportion of patients with treatment modifications during the COVID-19 lockdown in France was the primary end point of the study.

Investigators reported that modifications occurred in 27% of patients, including treatment interruptions for 15%, postponement for 32%, changes to the administration schedule for 19%, and adapted monitoring for 30%. Treatment modifications were more frequent in patients receiving single-agent immune checkpoint inhibition (49%) and targeted therapy–based combination therapy (47%; Table). Notably, shifts in administration schedule were more common in patients who initiated treatment during the lockdown (33.0% vs 15.6%).

Measuring “the psychological impact of the pandemic-related lockdown” on patients and medical oncologists was the secondary end point of COVIPACT. Patients were asked to fill out self-questionnaires on:
• impact of event scale–revised (IES-R),
• perceived stress (PSS),
• sleep difficulty severity/insomnia (ISI),
• quality of life (QOL), and
• cognitive complaint (FACT-COG).

Completed stress-related questionnaires were available for 93% of patients. Medical oncologists were also asked to complete self-questionnaires on PSS, as well as on professional accomplishment and personal efficiency.

Impact of Event Results

Posttraumatic stress questionnaires—corresponding to stress related to the event—contained 22 items and used IES-R which categorized results as high, medium, or low stress. Results from this questionnaire showed that patients with cancer who were subject to COVID-19–related oncological treatment modifications experienced higher stress; specifically, of the 152 patients who experienced modification, 27% experienced high stress compared with 19% of the 423 patients whose therapeutic course was not altered ($P = .049$).

Further, low stress levels per IES-R were also slightly elevated among patients who experienced a treatment modification versus those who did not (35% vs 32%). “We assessed the pandemic-induced therapeutic modifications of patients’ cancer treatment and the psychological impact on patients and caregivers,” said Joly, head of medical oncology at François Baclesse Cancer Centre in Caen, France. Findings from the baseline analysis indicate that treatment modifications have a “negative impact on stress” in patients, she added.
In contrast with the high and low findings in the IES-R questionnaire, medium stress levels were more prevalent among patients who did not have a treatment modification versus those who did (49% vs 38%). Overall, 46% of the 575 questionnaire responders said they experienced medium stress. Low stress related to the event accounted for 33% of the questionnaire responses; high, 21%.

**PATIENT-REPORTED STRESS, INSOMNIA, QOL**

The stress patterns in the IES-R analysis were also present in the PSS evaluation. In the 571 completed PSS questionnaires, 48%, 46%, and 6% of the responses indicated low, medium, and high levels of perceived stress, respectively. Just as treatment modifications led to a greater likelihood that patients would report high event-related stress, they also predisposed patients to experience higher perceived stress. Nine percent of patients whose treatment was changed said they had high perceived stress compared with 5% of patients whose treatment was not altered (P = .061).

Low levels of perceived stress remained slightly elevated among patients with modifications (50% vs 47%), whereas medium levels were more common among patients who did not experience a treatment modification compared with those who did (49% vs 41%, respectively).

A total of 570 patients responded to the insomnia questionnaire. Those who did not have a treatment modification were moderately less likely to have no or slight insomnia (77% vs 75%). The opposite was true for moderate or severe insomnia, which affected 23% of patients with a modification and 23% without one, respectively.

Interestingly, despite their effects on patient-reported stress, COVID-19-related treatment modifications did not negatively affect patients’ QOL from a cognitive standpoint, Joly said. In both patients who did and did not experience treatment alterations, the FACT-COG QOL score was the same, 4.6 (P = .5).

**SENSE OF ACCOMPLISHMENT, STRESS BOTH HIGH AMONG HCPs**

Questionnaires from 73 respondents quantified the psychological impact of the COVID-19 quarantine on medical oncologists and oncology day care unit caregivers. The mostly female caregiver population (81%) comprised 35 nurses, 4 nursing assistants, 23 medical oncologists (including 1 hematologist), 5 residents, and 6 contributors in other qualifying but unspecified roles. The median age was 40 years (range, 22-63).

When evaluated in the caregiver cohort, PSS questionnaire results showed that health care providers (HCPs) were experiencing high levels of perceived stress, Joly said. The continuous PSS score was 16.3 (± 7.1). When stratified by high, medium, and low, the PSS scores were 10%, 53%, and 37%, respectively. Most respondents (56%) felt a low level of emotional exhaustion.

Despite observed stress, HCPs reported high levels of professional accomplishment and personal self-efficacy, noted Joly. Specifically, 60% said they felt a high sense of professional accomplishment. Thirty-three percent felt a medium level of personal accomplishment, and only 7% reported a low perception of accomplishment. Data also showed that the personal self-efficacy score was 32.8 (of 40.0; ± 4.5).

Patients and participating HCPs were asked to respond to the questionnaires at not only baseline but also 3- and 6-month follow-ups. Following the presentation of the baseline findings on patient stress and other cognitive and QOL-related factors, the next step in the COVIPACT study is “evaluating the evolution of psychosocial parameters over these 2 periods after the lockdown among patients and caregivers,” Joly said.

These data are expected to shed light on the longer-term magnitude of treatment modifications on patients with cancer, as well as the determinants of posttraumatic stress for both patients and providers. In the meantime, oncology centers should seek to establish psychosocial support resources for patients receiving active therapy in an effort to minimize IES-R, Joly concluded.

### TABLE. Treatment Modifications Observed in the COVIPACT Study

<table>
<thead>
<tr>
<th>Treatment description</th>
<th>Patients who experienced a treatment modification (n = 165)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy alone</td>
<td>18%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chemotherapy plus other</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy plus other</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy alone</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Line of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>21%</td>
<td>.007</td>
</tr>
<tr>
<td>Relapsed setting</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Primary tumor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>27%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Digestive</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Lung, head, and neck</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Urologic, genital</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

**REFERENCE**


**MORE ON OncLive.com**

Experts Consider Long-Term Impact of COVID-19 on Oncology Care

Investigators conducted a survey involving health care representatives from the international oncology community to assess the preliminary effects of the coronavirus disease 2019 (COVID-19) pandemic and highlight major concerns regarding patient care.

“When you look into the future, the expected problem is the risk of delayed diagnoses of new cancer,” said Guy Jerusalem, MD, PhD, during a presentation at the European Society for Medical Oncology Virtual Annual Congress 2020. “The economic consequences of COVID-19, which can affect access to health care and cancer treatments, have to be carefully evaluated.”

FOR MORE VISIT: [https://bit.ly/3iZuKxA](https://bit.ly/3iZuKxA)
RESEARCH ON CHIMERIC ANTIGEN receptor (CAR) T-cell therapies has exploded since the first such treatment received approval in 2017. Hundreds of trials are under way, 3 therapies for hematologic malignancies are on the market, and 2 new products may receive FDA approval in the near future, including a BCMA-directed therapy that is poised to help transform treatment of multiple myeloma (MM).

In the near term, the approved therapies will gradually gain more indications and move to earlier treatment stages, experts say. On a parallel track, an off-the-shelf allogeneic product that is less costly and time-consuming to produce could be approved within a few years, greatly expanding the number of patients benefiting from CAR T cells. Other new categories of cellular therapies, such as tumor-infiltrating lymphocytes (TILs) that treat solid tumors, are also moving through the development pipeline.

The recent surge in research has been accompanied by a diversification of development and manufacturing pathways for these complex, personalized immunotherapies. Big pharmaceutical companies, start-ups, medical centers, and government labs alike are producing CAR T cells. Decentralized point-of-care processing and improved “cell engineering in a box” technologies may eventually speed up production and bring cellular therapies to more sites closer to patients.

“There’s a lot of innovation happening and a lot investment, and it’s really exciting. Before there were a few labs, and now we have a whole set of industries,” CAR T-cell pioneer Carl H. June, MD, said in an interview with OncologyLive®. A 2015 Giants of Cancer Care® award winner, June is the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine and director of the Parker Institute for Cancer Immunotherapy, both at the University of Pennsylvania in Philadelphia.

The number of clinical trials evaluating CAR T-cell therapies has increased dramatically since 2015, when investigators counted a total of 78 studies registered on the ClinicalTrials.gov website. In June 2020, the site listed 671 trials, comprising 357 registered in China, 256 in the United States, and 58 in other countries (TABLE).¹

THE CD19–DIRECTED LANDSCAPE
So far, the FDA has approved 3 CAR T-cell treatments, all directed at CD19. The first was tisagenlecleucel (tisa-cel; Kymriah), initially approved in August 2017 for refractory or relapsed B-cell acute lymphoblastic leukemia (R/R ALL) in patients up to 25 years old and later expanded to include adults with R/R large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL). The approvals are based on research June and colleagues conducted.² ³

In October 2017, axicabtagene ciloleucel (axi-cel; Yescarta) gained approval for adults with R/R DLBCL, primary mediastinal B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL). In July 2020, brexucabtagene autoleucel (brexu-cel; Tecartus) joined the roster with an accelerated approval for adults with R/R mantle cell lymphoma; continued approval may be contingent on a confirmatory trial.⁴
Another CD19-directed therapy for R/R large B-cell lymphoma, lisocabtagene maraleucel (liso-cel; JCAR017), was under FDA review at press time, with a goal date of November 16, 2020. The application is based on the phase 1 TRANSCEND-NHL-001 study (NCT02631044), whose results showed an objective response rate (ORR) of 73% (95% CI, 66.8%-78.0%), including a complete response (CR) rate of 53% (95% CI, 46.8%-59.4%) among 256 evaluable patients. Median duration of response (DOR) was not reached (NR; 95% CI, 8.6-NR) with 12.0 months of median follow-up. Median progression-free survival was 6.8 months (95% CI, 3.3-14.1), and the median overall survival was 21.1 months (95% CI, 13.3-NR).

Safety analysis showed 79% of patients in the safety population (n = 269) had grade 3 or higher treatment-emergent adverse effects (TEAEs), primarily cytopenias (neutropenia, 60%; anemia, 37%; thrombocytopenia, 27%). Cytokine release syndrome (CRS) and neurological events occurred in 42% and 30% of patients, respectively. These effects included grade 3 or higher CRS in 2% of patients and neurological events in 10%.

Differences in trial design and patient cohorts make comparisons with other CAR T-cell therapies difficult, but liso-cel appears to have an impressive toxicity profile and good durability, said Andre H. Goy, MD. Goy is physician in chief at Hackensack Meridian Health Oncology Care Transformation Service, chairman and chief physician officer at John Theurer Cancer Center, Lydia Pfund Chair for Lymphoma, academic chairman oncology at Hackensack Meridian School of Medicine at Seton Hall University, and professor of medicine at Georgetown University in Washington, DC.

“Liso-cel’s impact is going to be significant because if it’s confirmed to be less toxic, as it looks like, and assuming there are no issues with the manufacturing process, this could definitely be a competitor. No question about that,” Goy, a leading investigator of brexucel and other CAR therapies, said in an interview.

**TARGETING BCMA**

Also in late-stage development is idecabtagene vicleucel (ide-cel; bb2121), with an

<table>
<thead>
<tr>
<th>TABLE. A Snapshot of the CAR T-Cell Therapy Landscape</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chimeric antigen receptor T cell</strong></td>
</tr>
<tr>
<td><strong>scFv</strong> single-chain variable fragment</td>
</tr>
<tr>
<td><strong>Sator</strong> Chimeric antigen receptor</td>
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<tr>
<td><strong>Transmembrane domain</strong></td>
</tr>
<tr>
<td><strong>CD20</strong></td>
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<tr>
<td><strong>Co-stimulatory domain</strong></td>
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<tr>
<td><strong>4-1BB</strong></td>
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<tr>
<td><strong>CD19 chain (activator)</strong></td>
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</tbody>
</table>

The 3 CAR T-cell therapies approved by the FDA share similar structures, with a single-chain variable fragment (sc-FV) directed at the CD19 antigen.

**FDA approvals for CAR T-cell therapies**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Approval Date</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel (Kymriah)</td>
<td>August 30, 2017</td>
<td>For patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse</td>
</tr>
<tr>
<td>Axicabtagene ciloleucel (Yescarta)</td>
<td>October 18, 2017</td>
<td>For adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from FL</td>
</tr>
<tr>
<td>Brexucabtagene autoleucel (Tecartus)</td>
<td>July 24, 2020</td>
<td>Accelerated approval for adults with R/R mantle cell lymphoma (may be contingent on a confirmatory trial)</td>
</tr>
</tbody>
</table>

**Pending BLAs**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Approval Date</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisocabtagene maraleucel (JCAR017)</td>
<td>November 16, 2020</td>
<td>FDA goal date for decision on BLA for adults with R/R large B-cell lymphoma after ≥ 2 prior therapies</td>
</tr>
<tr>
<td>Idecabtagene vicleucel (ide-cel; bb2121)</td>
<td>March 27, 2021</td>
<td>FDA goal date for decision on BLA for adults with multiple myeloma who have received ≥ 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody</td>
</tr>
</tbody>
</table>

**In the pipeline**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Approval Date</th>
<th>Indications</th>
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</thead>
<tbody>
<tr>
<td>Analysis shows 671 CAR T-cell clinical trials</td>
<td></td>
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<tr>
<td>357 in China</td>
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<tr>
<td>256 in United States</td>
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<tr>
<td>58 in other countries</td>
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<tr>
<td>Phases</td>
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<tr>
<td>China: phase 1, 306; phase 2, 19; phase 3, 1; N/A, 31</td>
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<tr>
<td>United States: phase 1, 209; phase 2, 25; phase 3, 4; N/A, 18</td>
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<tr>
<td>Other countries: phase 1, 42; phase 2, 7; phase 3, 1; N/A, 8</td>
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<tr>
<td>Targets</td>
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<tr>
<td>Hematologic malignancies: CD19, followed by BCMA, CD22, CD20, CD38, CD123, CD30, CD138, CD133, CD4, and CD7</td>
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</tr>
<tr>
<td>Solid tumors: mesothelin, followed by MUC1, GP53, CD2, HER2, EGFR, EGFR VIII, PSMA, EpCAM, Claudin 18, CEA, and CD276</td>
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</table>

BLA, biologics license application; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; N/A, not applicable; R/R, relapsed or refractory.
FDA decision expected by March 27, 2021. The biologics license application seeks approval for the BCMA-directed CAR therapy for the treatment of adult patients with MM who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.8

The application is supported by data from the phase 2 KarMMA trial (NCT03361748) in heavily pretreated patients (N = 128) with refractory MM.2 Treatment with ide-cel resulted in an ORR of 73% (95% CI, 65.8%-81.1%; P < .0001), meeting the trial’s primary end point, according to findings presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program. The CR/stringent CR rate was 33% (95% CI, 24.7%-40.9%; P < .0001), the median DOR was 10.7 months (95% CI, 9.0-11.3), and median progression-free survival was 8.8 months (95% CI, 5.6-11.6).9

Grade 3 or higher CRS occurred in 5.5% of patients, and 1 death occurred because of a CRS event. Grade 3 neurotoxicity events occurred in 3.1% of patients. No grade 4 or 5 events were reported. Grade 3 or worse CRS or neurotoxicity events were reported in 6% or less of patients at the target dose of 450 x 10⁶ CAR T cells. Any-grade CRS and neurotoxicity events occurred in 84% and 18% of patients, respectively.9

Therapies targeting BCMA are expected to have a significant impact on the treatment landscape in MM. The transmembrane glycoprotein is expressed at high levels on MM cells and on plasma cells but not on other normal tissue, making it a promising target.10 In August 2020, the FDA approved the first therapy targeting BCMA, the antibody-drug conjugate belantamab mafodotin-blmf (Blenrep), for patients with R/R MM who have received at least 4 prior therapies.2

Approval of ide-cel or another similar CAR T-cell therapy would be a “huge event” because it would fulfill a major unmet medical need and show that CARs work with targets other than CD19, according to June. “What the field definitely needs is curative therapy so patients aren’t on chronic treatment. It’s really exciting that that’s going to happen,” he said.

June added that he anticipates many trials will look at whether CAR treatments could replace stem cell transplants for patients with MM and, eventually, whether CARs can be used as frontline therapy for the disease.

**PENDING STUDIES**

Studies are already under way on using other CARs earlier in treatment paradigms. The phase 3 ZUMA-7 trial (NCT03391466) is evaluating axi-cel versus standard-of-care second-line therapy for patients with R/R DLBCL, and the phase 2 ZUMA-12 trial (NCT03761056) is studying the therapy as a frontline treatment for high-risk large B-cell lymphoma. The phase 2 TRANSCEND-PILOT-017006 trial (NCT03483103) is testing liso-cel as a second-line therapy for patients with aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for stem cell transplant. “A lot of studies are investigating the best timing for CAR T,” Goy said. “We’re looking at shifting [CARs] to a better, earlier use because we know that although patients respond even if they have failed multiple lines of therapy, if they have [a large burden of] disease and are kind of beat up by the prior treatment or lymphoma, they don’t do as well.”

Renier J. Brentjens, MD, PhD, a leading CAR T-cell investigator, also sees opportunities to move the therapies forward. “In the arena of, for example, DLBCL, where there are a significant number of durable remissions, I would not be surprised if [a CAR T-cell therapy] becomes kind of a second-line drug as opposed to the drug of last resort,” said Brentjens, director of the Cellular Therapeutics Center at Memorial Sloan Kettering Cancer Center in New York, New York.

Investigators are also conducting trials of CD19-directed CAR T-cell therapies against new indications, such as B-cell ALL in adults and low-grade lymphomas such as FLs and chronic lymphocytic lymphoma. Kite Pharma has filed a supplemental biologics license application with the FDA to expand axi-cel’s indications by adding R/R FL and marginal zone lymphoma following 2 or more systemic therapies, based on data from the phase 2 ZUMA-5 trial (NCT03105336).11

Investigators are also studying existing CARs in combination with checkpoint inhibitors and other immunotherapy drugs.

Beyond liso-cel and ide-cel, dozens of enhanced CARs directed at CD19 and BCMA have shown promise and a few could be commercialized within 2 or 3 years. One is JNJ-4528, which is directed against 2 distinct BCMA epitopes. It was originally developed in China (where it is called ciltacabtagene autoleucel) and is now being developed through a collaboration between Legend Biotech and Janssen Biotech. The agent has shown positive results for patients with R/R MM in phase 1 and 2 trials and been granted breakthrough therapy designation in the United States and China, as well as PRIME status from the European Medicines Agency.12

A number of novel CARs with different targets and formulations are in trials, but when they might become widely available is unclear. These include innovations such as bispecific or dual CAR T-cell therapies targeting CD19-CD22 or BCMA-CD3, “armored CARs” that secrete cytokines, and CARs aimed at solid tumors.

**OFF-THE-SHELF CARS**

The next major CAR development may instead be an allogeneic, off-the-shelf product that uses donor T cells.

Goy said allogeneic products are among the most promising of the next wave of CAR treatments. “They’re off-the-shelf by definition, and very fit T cells. It’s very early but so far the responses have been very impressive, based on small numbers of patients, and not very toxic. That will be potentially very important,” he said.

June called an allogeneic CAR a potential “game changer” because it can be manufactured in large batches and delivered to patients anywhere for immediate infusion, at a significantly lower cost than that of current CAR therapies. He said these therapies could arrive in as soon as 3 years.

“Once allogeneic cell [therapies] come out, they’ll be everywhere and have much deeper penetration into smaller centers, more rural areas where people have no access to CAR T cells right now. All the small practices can just order them. That will be the tipping point for the field,” he said.
point. Right now it will stay at the major centers for these autologous cells," June said.

Among the more advanced allogeneic therapies are UCART19 and ALLO-501, anti-CD19 CARs that Allogene and partner firms are developing. The 2 agents are structurally identical but use different manufacturing processes and are paired with different lymphodepletion regimens.13

In pooled data from 2 phase 1 studies (CALM; NCT02746952 and PALL; NCT02808442), 82% (14 of 17) of patients with R/R B-ALL who received UCART19 and a lymphodepletion regimen containing fludarabine, cyclophosphamide, and alemtuzumab achieved CR or CR with incomplete hematologic recovery.14

In the phase 1ALPHA study (NCT03939026), ALLO-501 was administered after a lymphodepletion regimen of fludarabine, cyclophosphamide, and anti-CD52 the monoclonal antibody ALLO-647 to patients with previously treated R/R large B-cell lymphoma or FL. The ORR was 63% (95% CI, 38%-84%), including a CR of 37% (95% CI, 16%-62%) in 19 evaluable patients.15

The companies developing UCART19/ ALLO-501 have several allogeneic candidates, including an anti-BCMA MM therapy (ALLO-715). Meanwhile, Cellectis is trial-
ing UCART123, a CD123-targeted therapy for R/R acute myeloid leukemia, in the phase 1 AMELI-01 study (NCT03190278).

Other allogeneic CAR T-cell therapies in trials include 3 from Precision BioSciences: a CD19-directed product (PBCAR0191) being studied for no-Hodgkin lymphoma (NHL) and ALL; a CD20-targeted therapy (PBCAR20A) for NHL, chronic lymphocytic leukemia, and small lymphocytic lymphoma; and an anti-BCMA therapy for MM (PBCAR269A).16

Caribou Biosciences’ CB-010, an anti-CD19 therapy for R/R B-cell NHL, is slated to launch the phase 1 ANTLER trial soon.17

Off-the-shelf CAR therapies will eventually coexist with the personalized autologous therapies, predicted Jason Bock, PhD, vice president of the Therapeutics Discovery division and head of biologics product development at The University of Texas MD Anderson Cancer Center in Houston. “It will be dramatically more accessible, dramatically less costly, and probably a little bit less efficacious. There will be a lot of investment in technology to figure out how to try to bridge that gap. What you’ll lose in terms of pure potency, you’ll probably gain in terms of consistency,” he said.

Bock and others said they look forward to someday seeing CARs for solid tumors, but investigators face several biological hurdles, and marketable products are at least 5 years away. However, other types of adoptive cell therapies for solid tumors will likely become available much sooner. Iovance Biotherapeutics expects to file an application during 2021 for lifileucel, a TIL therapy for metastatic melanoma that is also being studied in cervical cancer.18

As development of CARs and related therapies has mushroomed, research and manufacturing have moved from a small number of academic-industry partnerships into a variety of venues. Commercial T-cell products are manufactured at large pharmaceutical company hubs, and therapies for trials are being produced at those sites, at specialized contract labs, and at several major medical centers, such as Memorial Sloan Kettering, Dana-Farber Cancer Institute, MD Anderson, Stanford Medicine, and Moffitt Cancer Center.

Bock said MD Anderson recently added its production capacity by purchasing a 60,000-square-ft cellular therapy manufacturing facility at Texas Medical Center and Moffitt Cancer Center. Bock said MD Anderson’s new facility will not be used for long-term manufacturing of commercialized CAR products, which is better left to pharmaceutical companies that are experts in large-scale production, distribution, and marketing, he said.

However, Bock and others said they can envision a time when fully enclosed, automated "cell engineering in a box" systems are perfected and installed at medical centers, allowing point-of-care CAR T-cell production. Technicians would essentially insert patient cells, viral vectors, and other supplies in one end and wait for a bag of engineered cells to come out the other for infusion. Investigators have experimented with such systems, using the Miltenyi CliniMACS Prodigy device to produce CAR T-cells and treating patients with hematological malignancies.20,21

Brentjens said there may not yet be enough published data to conclude that automated systems are feasible, and he does not know what training would be required of hospital staff. He also noted that the hospital would still have to purchase viral vectors from a pharmaceutical company to make the process work.

"It’s like cake mix. You can either buy a fully made cake, or in that paradigm you’re buying the cake mix and you’re cooking up the cake yourself," he said. “But obviously, the cake mix costs a lot less than the cake.”
In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:

29% reduction in risk of PFS event* 
(HR: 0.71; 95% CI: 0.54, 0.93; P = 0.011); median PFS 48.2 vs 20.8 months for A+CHP and CHOP, respectively; primary endpoint

*PFS was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease.

Indication
ADCETRIS® (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

Important Safety Information

BOXED WARNING
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Contraindication
ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

Warnings and Precautions
- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
ECHELON-2 trial design: A multicenter, phase 3, randomized, double-blind, double-dummy, actively controlled trial in 452 patients with sALCL and other CD30-expressing PTCL. Patients were randomized 1:1 to A+CHP (n = 226) or CHOP (n = 226), and received treatment every 3 weeks for 6 to 8 cycles at investigator’s discretion. Primary endpoint was PFS per IRF, defined as progression, death from any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease. Overall survival was a key secondary endpoint.2,3

Most common adverse reactions (≥20%) in combination with CHP

Anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.2

A+CHP = ADCETRIS + cyclophosphamide, doxorubicin, prednisone; ALCL = anaplastic large cell lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHP = cyclophosphamide, doxorubicin, prednisone; CI = confidence interval; HR = hazard ratio; IRF = independent review facility; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma.
**Important Safety Information, cont’d**

- **Anaphylaxis and infusion reactions:** Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS® (brentuximab vedotin). Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

- **Hematologic toxicities:** Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (>1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma or previously untreated PTCL.

  Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

- **Serious infections and opportunistic infections:** Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.

- **Tumor lysis syndrome:** Closely monitor patients with rapidly proliferating tumor and high tumor burden.

- **Increased toxicity in the presence of severe renal impairment:** The frequency of Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.

- **Increased toxicity in the presence of moderate or severe hepatic impairment:** The frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.

- **Hepatotoxicity:** Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- **PML:** Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

- **Pulmonary toxicity:** Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS during evaluation and until symptomatic improvement.

- **Serious dermatologic reactions:** Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- **Gastrointestinal (GI) complications:** Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

- **Embryo-fetal toxicity:** Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

**Most Common (≥20% in any study)**

**Adverse Reactions**

Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

**Drug Interactions**

Concomitant use of strong CYP3A4 inhibitors or inducers has the potential to affect the exposure to monomethyl auristatin E (MMAE).

**Use in Specific Populations**

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use. Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages and full Prescribing Information at [adcetrispro.com](http://wwwadcetrispro.com)

**References:**


NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
ACDTRIS® (brentuximab vedotin) for injection, for intravenous use
Initial U.S. approval: 2011

Brief Summary: see package insert for full prescribing information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
JC virus infection resulting in PML and death can occur in patients receiving ACDTRIS.

1 INDICATIONS AND USAGE
ACDTRIS is a CD19-directed antibody-drug conjugate indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD19-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
For dosing instructions of combination agents administered with ACDTRIS, see the manufacturer's prescribing information.

Administer ACDTRIS as a 30-minute intravenous infusion.

The recommended dose is 1.8 mg/kg up to a maximum of 180 mg in combination with cyclophosphamide, doxorubicin, and prednisone (CHP), administered every 3 weeks with each cycle of chemotherapy for 6 to 8 doses.

Reduce the dose to patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance [CrCl] <30 mL/min).

The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

2.2 Recommended Prophylactic Medications
In patients with previously untreated PTCL who are treated with ACDTRIS + CHP, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification
Peripheral Neuropathy: For Grade 2 motor neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 sensory neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks, for Grade 3 motor neuropathy, discontinue dosing. For Grade 4 sensory or motor neuropathy, discontinue dosing. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Neutropenia: For Grade 3 or 4 neutropenia, administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

4 CONTRAINDICATIONS
ACDTRIS is contraindicated with concomitant bortezomib due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

5 WARNINGS AND PRECAUTIONS
5.1 Peripheral Neuropathy
ACDTRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ACDTRIS-induced peripheral neuropathy is cumulative.

In ECHLON-2 (Study 8), 52% of patients treated with ACDTRIS + CHP experienced new or worsening peripheral neuropathy of any grade (by maximum grade, 54% Grade 1, 32% Grade 2, 13% Grade 3, <1% Grade 4). The peripheral neuropathy was predominantly sensory (84% sensory, 16% motor) and had a median onset time of 2 months (range, <1-5). At last evaluation, 50% had complete resolution of neuropathy, 12% had partial improvement, and 38% had no improvement. The median time to resolution or improvement was 4 months (range, 0-19). Of patients with residual neuropathy at their last evaluation, the neuropathy was Grade 1 in 72%, Grade 2 in 25%, and Grade 3 in 3%.

Monitor patients for symptoms of neuropathy, such as hyposthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathy pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ACDTRIS.

5.2 Anaphylaxis and Infusion Reactions
Infusion-related reactions, including anaphylaxis, have occurred with ACDTRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ACDTRIS and administer appropriate medical therapy.

If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxieties
Fatal and serious cases of febrile neutropenia have been reported with ACDTRIS. Prophylaxis (e.g., antibiotics) should be used for patients at risk for neutropenia. ACDTRIS should be discontinued in patients who develop neutropenia. Monitor patients with febrile neutropenia for clinical signs and symptoms of infection and administer appropriate antimicrobial therapy.

5.4 Infectious Complications
Monitor patients for infections. If infection occurs, treat appropriately. Infections may require discontinuation of ACDTRIS.

5.5 Hepatotoxicity
Fetal and serious cases of hepatic toxicity have occurred with ACDTRIS. Monitor patients for signs and symptoms of hepatic toxicity. In the event of new or worsening hepatic toxicity, hold ACDTRIS dosing until resolution. In the event of new or worsening hepatic toxicity, hold ACDTRIS dosing until resolution.

5.6 Gastrointestinal Complications
Monitor patients for gastrointestinal symptoms. If symptoms occur, treat appropriately. In the event of new or worsening gastrointestinal symptoms, hold ACDTRIS dosing until resolution.

5.7 Pulmonary Toxicity
Monitor patients for pulmonary toxicity. In the event of new or worsening pulmonary toxicity, hold ACDTRIS dosing until resolution.

5.8 Other Toxicities
Monitor patients for other toxicities. If toxicities occur, treat appropriately. In the event of new or worsening other toxicities, hold ACDTRIS dosing until resolution.

5.9 Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) has been reported with ACDTRIS. Monitor patients for symptoms of PML and hold ACDTRIS dosing if diagnosis of PML is confirmed.

5.10 Serious Dermatologic Reactions
Monitor patients for dermatologic reactions. If reactions occur, treat appropriately. In the event of new or worsening dermatologic reactions, hold ACDTRIS dosing until resolution.

5.11 Adverse Reactions
Monitor patients for adverse reactions. If reactions occur, treat appropriately. In the event of new or worsening adverse reactions, hold ACDTRIS dosing until resolution.

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

6 ADVERSE REACTIONS
6.1 Clinical Laboratory Changes

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment
The frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ACDTRIS in patients with moderate and severe hepatic impairment (Child-Pugh B or C).

5.8 Hepatotoxicity
Fetal and serious cases of hepatotoxicity have occurred in patients receiving ACDTRIS. Monitor patients for signs and symptoms of hepatic toxicity. In the event of new or worsening hepatotoxicity, hold ACDTRIS dosing until resolution.

5.9 Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) has been reported with ACDTRIS. Monitor patients for symptoms of PML and hold ACDTRIS dosing if diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity
Fetal and serious cases of noninfectious pulmonary toxicity including pneumonia, interstitial lung disease, and acute respiratory distress syndrome (ARDS) have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary toxicity, hold ACDTRIS dosing until resolution.

5.11 Serious Dermatologic Reactions
Fetal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ACDTRIS. Monitor patients for signs and symptoms of SJS or TEN, discontinue ACDTRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications
Fetal and serious cases of acute pancreatitis have been reported. Monitor patients for signs and symptoms of gastrointestinal toxicity. In the event of new or worsening gastrointestinal symptoms, hold ACDTRIS dosing until resolution.

5.13 Embryo-Fetal Toxicity
Based on animal data, ACDTRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ACDTRIS in pregnant women. Animals studies have shown no evidence of fetal toxicity. ACDTRIS should be administered to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.
The most common adverse reactions (≥20%) in combination with CHOP were anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

Previously Untreated sALCL or Other CD30-Expressing PTCL (Study 6, ECHENOL-2)

ADCCRTIS in combination with CHOP was evaluated in patients with previously untreated, CD30-expressing PTCL, in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. Patients were randomized to receive ADCCRTIS + CHOP or CHOP alone, for 6 to 8, 21-day cycles, ADCCRTIS was administered on Days 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHOP. The trial required hepatic transaminases ≤3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy.

A total of 448 patients were treated (223 with ADCCRTIS + CHOP, 226 with CHOP), with 6 cycles planned in 81%. In the ADCCRTIS + CHOP arm, 70% of patients received 6 cycles, and 18% received 8 cycles. Primary prophylaxis with G-CSF was administered to 94% of ADCCRTIS + CHOP-treated patients and 27% of CHOP-treated patients. Fatal adverse reactions occurred in 3% of patients in the CHOP arm and 4% of patients in the ADCCRTIS + CHOP arm, most often from infection. Serious adverse reactions were reported in 38% of ADCCRTIS + CHOP-treated patients and 35% of CHOP-treated patients. Serious adverse reactions occurring in >2% of ADCCRTIS + CHOP-treated patients included febrile neutropenia (14%), pneumonia (9%), pyrexia (4%), and sepsis (3%).

The most common adverse reactions observed ≥2% more in recipients of ADCCRTIS + CHOP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥1%) adverse reactions observed ≥2% more with ADCCRTIS + CHOP were febrile neutropenia, abdominal pain, decreased appetite, dyspepsia, edema, cough, dizziness, hypokalemia, decreased weight, and myalgia. In recipients of ADCCRTIS + CHOP, adverse reactions led to dose delays of ADCCRTIS in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCCRTIS + CHOP in 4% (most often from peripheral neuropathy and infection).

Table 7: Adverse Reactions Reported in ≥10% of ADCCRTIS + CHOP-Treated Patients Previously Untreated, CD30-Expressing PTCL (Study 6: ECHENOL-2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCCRTIS + CHOP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
<td>56</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Lymphopenia*</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Mucositis</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>28</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 7: Adverse Reactions, cont'd

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCCRTIS + CHOP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alginacia</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

* Derived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and end of treatment.

The table includes a combination of grouped and ungrouped terms. CHOP = cyclophosphamide, doxorubicin, and prednisone; CHOP + cetuximab = cyclophosphamide, doxorubicin, vincristine, and prednisone. Events were graded using the NCICTAE Version 4.03.

Additional Important Adverse Reactions

- Pneumonia
- Pulmonary toxicity
- Myelosuppression
- Anemia
- Diarrhea
- Fatigue
- Myalgia
- Nausea
- Vomiting
- Abdominal pain
- Peripheral neuropathy
- Headache
- Dizziness
- Fatigue
- Pyrexia
- Edema
- Upper respiratory tract infection

6.2 Post Marketing Experience

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

Blood and lymphatic system disorders: febrile neutropenia.

Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes).

Hepatic disorders: hepatotoxicity.

Infections: PMI, serious infections and opportunistic infections.

Metabolism and nutrition disorders: hyperkalemia.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS; some with fatal outcomes.

Skin and cutaneous disorders: Toxic epidermal necrolysis, including fatal outcomes.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADCCRTIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-breutuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies. A total of 58 patients were either transiently or persistently positive for anti-breutuximab vedotin antibodies; 26 (45%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-breutuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MVAAS, which may increase the risk of adverse reactions. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations. See Data. The available data from case reports on ADCETRIS use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15–20%, respectively.

Data

Animal Data

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1.3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 8 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (>99%), post-implantation loss (>99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and hypertrophied hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brentuximab vedotin 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 from ADCETRIS, including cytopenasia and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action.

Pregnancy Testing

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

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

Males

ADCETRIS may damage spermatogenesis and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility

Males

Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with CHP for patients with previously untreated, CD30-expressing PTCL (Study 6; EHELON-2), 91% of ADCETRIS + CHP-treated patients were age 65 or older. Among older patients, 74% had adverse reactions ≥ Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 82% had adverse reactions ≥ Grade 3 and 93% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 29% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (Creatinine Clearance [CrCl] < 30 mL/min). No dosage adjustment is required for mild (CrCl ≥ 30 to < 60 mL/min) or moderate (CrCl ≥ 15 to < 30 mL/min) renal impairment.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment.

10 OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

17 PATIENT COUNSELING INFORMATION

Peripheral Neuropathy: Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness.

Fever/Neutropenia: Advise patients to contact their health care provider if a fever of 100.3°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

Infusion Reactions: Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion.

Hepatotoxicity: Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Progressive Multifocal Leuкоencephalopathy: Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

Pulmonary Toxicity: Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath.

Acute Pancreatitis: Advise patients to contact their health care provider if they develop severe abdominal pain.

Gastrointestinal Complications: Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea.

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcertris.com.
Cemiplimab Demonstrates Frontline Potential in Advanced PD-L1+ NSCLC

by CAROLINE SEYMOUR

Cemiplimab (LIBTAYO) monotherapy led to a significant improvement in overall survival (OS) and progression-free survival (PFS) versus platinum-doublet chemotherapy as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) with PD-L1 expression on at least 50% of their tumor cells, according to findings from the second preplanned interim analysis of the phase 3 EMPOWER-Lung 1 trial that were presented during the European Society for Medical Oncology Virtual Congress 2020.

At a median follow-up of approximately 10 months in the intention-to-treat (ITT) population with PD-L1 expression of 50% or greater, the median OS was not reached (95% CI, 17.9-not estimable [NE]) in the cemiplimab arm versus 14.2 months (95% CI, 11.2-17.5) in the chemotherapy arm (HR, 0.57; 95% CI, 0.43-0.68; P < .001).

“Tumors are not just tumors, they are patients,” said Ahmet Sezer, MD, lead study author and professor in the Department of Medical Oncology at Baskent University in Ankara, Turkey. “Our data suggest that cemiplimab is a safe and effective treatment option for patients with advanced NSCLC with PD-L1 expression greater than or equal to 50%.”

For patients who do not have targetable mutations, PD-1 and PD-L1 inhibitors alone or in combination with chemotherapy are preferred therapeutic options. However, selecting the most effective treatment with minimal toxicity remains a challenge. Further, additional therapies with survival benefits and optimization of chemotherapy-free regimens are needed for patients with PD-L1 expression of at least 50%.

Cemiplimab is a high-affinity, highly potent, human PD-1 inhibitor approved for the treatment of patients with advanced cutaneous squamous cell carcinoma. In phase 1 and 2 studies, cemiplimab demonstrated antitumor activity with a safety profile similar to that described for other PD-1 inhibitors in advanced solid tumors, including NSCLC.

In EMPOWER-Lung 1 (NCT0308540) eligible patients had treatment-naive advanced NSCLC; PD-L1 expression of 50% or greater; no EGFR, ALK, or ROS1 mutations; and an ECOG performance status of 0 or 1. Patients with treated, clinically stable central nervous system metastases and controlled hepatitis B or C virus, or HIV were allowed on the study.

Patients in the ITT population were randomized 1:1 to 350 mg of intravenous cemiplimab monotherapy every 3 weeks (n = 356) or 4 to 6 cycles of investigator’s choice chemotherapy (n = 354). Patients in the cemiplimab arm were treated until progressive disease or up to 108 weeks. Upon progressive disease, patients in the cemiplimab arm had the option of continuing therapy plus 4 cycles of chemotherapy, and patients in the chemotherapy arm had the option of crossing over to the cemiplimab arm.

OS and PFS served as primary end points of the study. Secondary end points included objective response rate (ORR), duration of response (DOR), health-related quality of life (HRQOL), and safety.
All patients were subject to PD-L1 testing with the PD-L1 IHC 22C3 pharmDx assay. Those who underwent testing prior to August 2018 (n = 235) had to be retested per protocol for PD-L1 expression and grouped among those who had been tested after August 2018 (n = 475). The PD-L1 50% or greater ITT population comprised 563 patients, of whom 283 received cemiplimab and 280 received chemotherapy.

Baseline characteristics were well balanced between arms in the ITT and PD-L1 50% or greater ITT populations. In the ITT population, 11.7% of patients had brain metastases at baseline and 16.2% of patients had locally advanced disease, representing 2 patient subsets that have been historically underrepresented in clinical trials of first-line PD-1/PD-L1 inhibitors, said Sezer.

In the PD-L1 50% or greater ITT population, the ORR was 39.2% in the cemiplimab arm versus 20.4% in the chemotherapy arm (P < .0001). The median DOR was 16.7 months (range, 12.5-22.8) in the cemiplimab arm versus 6.0 months (range, 4.3-6.5) in the chemotherapy arm.

Additional analysis from the PD-L1 50% or greater ITT population showed that the 12-month OS rate was 72.4% in the cemiplimab arm versus 53.9% in the chemotherapy arm. The 24-month OS rates were 50.4% and 27.1%, respectively.

The 12-month PFS rate was 40.7% in the cemiplimab arm versus 7.1% in the chemotherapy arm. The 18-month PFS rates were 27.8% and NE, respectively.

**RESULTS IN THE ITT POPULATION**

At a median follow-up of 13.1 months in the ITT population, the median OS was 22.1 months (95% CI, 17.7-NE) with cemiplimab versus 14.3 months (95% CI, 11.7-19.2) with chemotherapy (HR, 0.68; 95% CI, 0.53-0.87; P = .0022). The 12-month OS rate was 70.3% in the cemiplimab arm versus 55.7% in the chemotherapy arm, and 24-month OS rates were 48.6% and 29.7%, respectively.

In the ITT population, the median PFS was 6.2 months in the cemiplimab arm versus 5.6 months in the chemotherapy arm (HR, 0.59; 95% CI, 0.49-0.72; P < .0001). The 12-month PFS rate was 37.8% in the cemiplimab arm versus 7.2% in the chemotherapy arm, and 18-month PFS rates were 28.0% and 3.9%, respectively.

“In both [the PD-L1 50% or greater ITT and overall ITT] populations, the PFS curves separate at approximately 6 months and remain well separated,” said Sezer.

**CORRELATING RESPONSES TO PD-L1 EXPRESSION**

Investigators also evaluated the delta in target tumor volume and ORR with baseline PD-L1 levels and found that higher PD-L1 expression correlated with improved responses to cemiplimab but not chemotherapy. The ORR with cemiplimab was highest in patients with PD-L1 expression of 90% or greater (45.9% vs 18.1%), followed by those in the 60% to 90% group (39.3% vs 20.0%), the 50% to 60% group (32.3% vs 22.9%), and the 50% or unknown group (21.6% vs 26.0%).

Sezer also noted that PFS and OS curves favored cemiplimab, regardless of PD-L1 expression level. Moreover, higher PD-L1 expression was associated with improved PFS and OS with cemiplimab but not chemotherapy.

**QUALITY OF LIFE**

Regarding HRQOL, patients in the cemiplimab arm experienced a clinically meaningful improvement in Global Health Status/HRQOL, which was defined as at least a 10-point increase from baseline. Among 355 patients who received cemiplimab, 139 remain on treatment and 6 completed treatment. A total of 210 patients discontinued treatment due to progressive disease (n = 133), death (n = 29), adverse effects (AEs; n = 23), patient decision (n = 9), withdrawn consent (n = 8), physician decision (n = 5), and lost follow-up (n = 3).

Among 342 patients who received chemotherapy, 45 remain on treatment and 149 completed treatment. A total of 148...
patients discontinued treatment due to progressive disease (n = 84), death (n = 25), AEs (n = 14), patient decision (n = 7), withdrawn consent (n = 9), physician decision (n = 5), and lost follow-up (n = 4).

The majority of patients who progressed on chemotherapy (n = 150; 73.9%) received cemiplimab as a crossover treatment. Additionally, 31.6% of patients who progressed on cemiplimab (n = 50) received extended cemiplimab treatment with the addition of chemotherapy. The median duration of treatment with cemiplimab was 27.3 months (range, 0.3-115.0) versus 17.7 months (range, 0.6-86.7) with chemotherapy.

Grade 3 or greater treatment-emergent AEs (TEAEs) occurred in 37.2% of patients in the cemiplimab arm versus 48.5% in the chemotherapy arm. Grade 3 or greater treatment-related AEs (TRAEs) occurred in 14.1% of patients in the cemiplimab arm versus 39.2% in the chemotherapy arm. Fatal TEAEs and TRAEs were comparable in both arms, at approximately 9.0% and 2.0% each, respectively.

Grade 3 or greater AEs that occurred in the cemiplimab and chemotherapy arms, respectively, included anemia (3.4% vs 16.4%), pneumonia (4.8% vs 5.6%), fatigue (1.1% vs 1.5%), decreased appetite (0.6% vs 0.3%), nausea (0% vs 1.2%), vomiting (0% vs 1.2%), thrombocytopenia (0% vs 8.2%), neutropenia (0.6% vs 10.2%), decreased platelet count (0% vs 3.5%), alopecia (0% vs 0.6%), peripheral neuropathy (0.3% vs 0.3%), and decreased neutrophil count (0.3% vs 5.3%).

“The safety profile of cemiplimab was consistent with the previously reported profile for cemiplimab and other PD-1/PD-L1 inhibitors in NSCLC and other tumor types,” said Sezer. “[Although patients had] substantially longer exposure to cemiplimab, [its] safety profile...appeared to be better than chemotherapy.”

For a full list of references, see the article at https://bit.ly/33ZsvG8.

Osimertinib Improves CNS Disease-Free Survival in Early EGFRm NSCLC

by JASON HARRIS

OSIMERTINIB (TAGRISSO) REDUCED

the risk for central nervous system (CNS) death or progression by 82% in patients with early-stage EGFR-mutated non–small cell lung cancer (NSCLC) following complete tumor resection, according to findings from the ADAURA trial presented at the European Society for Medical Oncology Virtual Congress 2020.

Masahiro Tsuboi, MD, PhD, a principal investigator for the trial, said based on these data, adjuvant osimertinib would be an effective and practice-changing treatment in this setting.

Tsuboi, chief and director of the Division of Thoracic Surgery and Oncology at the National Cancer Center Hospital East in Chiba, Japan, added that treatment with osimertinib was associated with fewer locoregional and distant relapses, a lower incidence of metastatic disease among patients who did have relapse, and fewer CNS recurrence events.

“The reduced risk of local and distant recurrence and improved CNS disease-free survival [DFS] reinforce adjuvant osimertinib as a highly effective, practice-changing treatment,” Tsuboi said during a presentation of the data.

In results from the ADAURA trial (NCT02511106), simultaneously published in the New England Journal of Medicine, adjuvant osimertinib demonstrated a clinically meaningful improvement in CNS disease-free survival (DFS) compared with placebo (HR, 0.18; 95% CI, 0.10-0.33; P < .0001; TABLE).1,2

The median CNS DFS was not reached in the experimental arm compared with 48.2 months in the placebo arm (HR, 0.18; 95%, 0.10-0.33; P < .0001).

In total, 45 patients had CNS DFS events, 6 (2%) with osimertinib and 39 (11%) with placebo. Of those who had recurrence, 4 (1%) in the osimertinib arm experienced CNS recurrence versus 33 (10%) in the placebo arm. “[These data also show] that patients who received osimertinib had fewer local/regional and distant relapses than those who received placebo,” Tsuboi said. Eleven percent of patients in the osimertinib arm had metastatic recurrence compared with 61% in the placebo arm.

Investigators concluded that the estimated probability of observing CNS recurrence at 18 months was less than 1% with osimertinib (95% CI, 0.2%-2.5%) versus 9% (95% CI, 5.9%-12.5%) with placebo.

Eleven percent of patients in the experimental arm had a DFS event compared with 46% in the placebo arm. Overall, 38% of patients assigned to osimertinib had metastatic recurrence compared with 61% in the placebo arm.

In the international, randomized, placebo-controlled, double-blind, phase 3 trial, 682 patients with primary nonsquamous stage IB to IIIA NSCLC harboring EGFR mutations, with exon 19 deletions or L858R mutations, were assigned to 80-mg once-daily osimertinib (n = 339) or placebo (n = 343). Patients received treatment for 3 years, or until disease recurrence or discontinuation criteria were met.

The primary end point was investigator-assessed DFS in patients with stage II to IIIA disease. Secondary end points comprised DFS in the overall population; DFS at 2, 3, 4, and 5 years; overall survival (OS); safety; and quality of life.

Inclusion criteria comprised patients who had and had not previously received adjuvant

For a full list of references, see the article at https://bit.ly/33ZsvG8.
chemotherapy. Patients had to be aged at least 18 years, have a World Health Organization performance status of 0 or 1, brain imaging if it was not completed in the preoperative setting, undergone complete resection with negative margins, and a maximum interval between surgery and randomization of either 10 weeks without adjuvant chemotherapy or 26 weeks if they had undergone adjuvant chemotherapy. Approximately 10% to 15% of patients with NSCLC in the United States and Europe and 30% to 40% of patients in Asia have EGFR-mutated NSCLC. These patients are particularly sensitive to treatment with EGFR-tyrosine kinase inhibitors (TKIs). Osimertinib is a third-generation, irreversible EGFR-TKI with clinical activity against CNS metastases.

On October 20, 2020, the FDA granted a priority review designation for a supplemental new drug application for osimertinib for the adjuvant treatment of patients with stage IB, II, and IIIA EGFR-mutated NSCLC following complete resection with curative intent. Data from ADAURA, presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, demonstrated that adjuvant osimertinib induced statistically significant and clinically meaningful improvement in DFS. Osimertinib reduced the risk for disease recurrence or death by 79% (HR, 0.21; 95% CI, 0.16-0.28; P < .0001).3 Osimertinib was associated with superior DFS rates at 1 (97% vs 69%), 2 (89% vs 53%), and 3 years (79% vs 41%). In April 2020, an independent data monitoring committee recommended that the trial be stopped 2 years early based on the efficacy findings. Osimertinib is approved by the FDA for the first-line treatment of patients with locally advanced or metastatic EGFR-mutant NSCLC and the treatment of locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

For a full list of references, see the article at https://bit.ly/3jYXA4l.
prognosis. Sacituzumab govitecan is a first-in-class Trop-2-directed ADC, with an antibody that is highly specific for Trop-2 and a high drug-to-antibody ratio. Additionally, it has an SN-38 payload, which is more potent than irinotecan, the parent compound.

**ASCENT TRIAL DESIGN**

ASCENT investigators randomized 529 patients with metastatic TNBC 1:1 to receive either sacituzumab govitecan (n = 267) or physician’s choice of treatment (n = 262) until disease progression or unacceptable toxicity. Sacituzumab govitecan was administered at 10 mg/kg intravenously on days 1 and 8 in 21-day cycles. Physician's choice of treatment included eribulin (n = 139), vinorelbine (n = 52), gemcitabine (n = 38), and capecitabine (n = 33).

Patients were stratified by the number of prior chemotherapies received (2-3 vs >3), geographic region, and the presence or absence of known brain metastases.

The primary end point of the trial was PFS; secondary end points included PFS for the full population, OS, objective response rate (ORR), duration of response (DOR), time to response, and safety. The PFS analysis was based on a central assessment in the brain metastases-negative population using a stratified log-rank test; there was a predefined maximum 15% cap for patients with brain metastases. Additionally, the safety population included all patients, regardless of brain metastases status, who received at least 1 dose of study treatment (n = 258 for sacituzumab govitecan; n = 224 for chemotherapy). The data cutoff date was March 11, 2020.

Demographics and patient characteristics were well balanced between the 2 arms. The majority of patients were female (99.5%), the median age was 53.5, and 79.5% of patients were White. More than half (56%) of patients had an ECOG performance status of 1, and 7.5% harbored BRCA1/2 mutations.

The median number of prior antirnucancer therapies was 4; the most common were taxane (100%), anthracycline (82%), cyclophosphamide (82%), carboplatin (66%), and capecitabine (Xeloda; 65.5%). PARP inhibitors and checkpoint inhibitors were previously administered in 7.5% and 27.5% of patients, respectively. The most common sites of disease were in the lung (44%), liver (42.5%), and bone (22%).

A total 213 and 201 patients in the sacituzumab govitecan and chemotherapy arms discontinued treatment, respectively, most frequently due to disease progression (199 and 166, respectively). Fifteen patients receiving sacituzumab govitecan and 0 patients on chemotherapy remain on treatment.

Additional results showed that through investigator assessment, sacituzumab govitecan led to a 65% reduction in the risk of disease progression or death (HR, 0.35); in the overall population, which included patients with brain metastases, the HR was 0.42, Bardia noted.

The PFS benefit was observed across prespecified subgroups, including age, race, number of prior therapies, geographic region (HR, 0.44 for North America vs 0.36 for rest of world), prior immunotherapy (HR, 0.37), liver metastases (HR, 0.48), and initial diagnosis of TNBC (HR, 0.38). In detail, the race subgroup comprised White (HR, 0.39), Black (HR, 0.45), and Asian (HR, 0.40) patients. Patients who received 2 to 3 prior therapies had improved PFS (HR, 0.39), as did those who received more than 3 treatments (HR, 0.48).

The ORR was 35% with sacituzumab govitecan, which comprised a 4% complete response (CR) rate and a 31% partial response (PR) rate; the ORR with standard treatment was 5% with a 1% CR rate and 4% PR rate (P < .0001). The clinical benefit rate was 45% with sacituzumab govitecan and 9% with standard treatment (P < .0001). The median DOR was 6.3 months (95% CI, 5.5-9.0) and 3.6 months (95% CI, 2.8-not estimable), respectively (P = .057).

Sacituzumab govitecan was given for a median 7 treatment cycles and a median treatment duration of 4.4 months (range, 0.03-22.9). Regarding safety, the most common, all-grade treatment-related adverse effects (TRAEs) with sacituzumab govitecan and chemotherapy included neutropenia (63% vs 43%, respectively), anemia (34% vs 24%), diarrhea (59% vs 12%), nausea (57% vs 26%), fatigue (45% vs 30%), and alopecia (46% vs 16%).

The key grade 3 or higher TRAEs in the sacituzumab govitecan and chemotherapy arms were neutropenia (46% vs 27%, respectively), diarrhea (10% vs < 1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (5% vs 2%). Granulocyte colony-stimulating factors were used in 49% and 23% of patients in the sacituzumab govitecan and standard therapy arms, respectively. Additionally, no severe cardiovascular toxicity was reported, nor reports of neuropathy above grade 2 and interstitial lung disease above grade 3 with sacituzumab govitecan.

Adverse effects that led to treatment discontinuation occurred in 4.7% and 5.4% of patients on sacituzumab govitecan and on chemotherapy, respectively; 0 and 1 treatment-related deaths, respectively, were reported.

A supplemental biologics application seeking full approval for the agent is planned for later this year, according to Immunomedics.

Ongoing studies are exploring sacituzumab govitecan in the neoadjuvant and adjuvant treatment settings and in combination with other targeted agents. Additionally, the ongoing, phase 3 TROPiCS-02 trial (NCT03901339) is evaluating the ADC in patients with hormone receptor-positive, HER2-negative breast cancer.

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- Examine the role of \textit{BRAF} mutations in treatment decisions for stage III and IV melanoma
- Assess the clinical evidence from phase 3 clinical trials

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Dose-Dense Chemotherapy Fails to Top Standard in Epithelial Ovarian Cancer

by BRIELLE BENYON

INCORPORATION OF WEEKLY DOSE-DENSE chemotherapy is not superior to standard 3-weekly chemotherapy for patients with epithelial ovarian cancer. Both progression-free survival (PFS) and overall survival (OS) data failed to show improvement over the standard of care. However, results from the ICON8 presented at the European Society for Medical Oncology Virtual Congress 2020 showed that the dose-dense regimen is safe and effective.¹

"[For] most of the past 3 decades, platinum-paclitaxel doublet chemotherapy administered on an once-every-3-weeks schedule for 6 to 8 cycles has been cornerstone in the first-line modality management of epithelial ovarian cancer," said Andrew Clamp, BMBCh, MSc Oncology, MRCP, PhD, chief investigator of the ICON8 study and senior lecturer and honorary consultant in medical oncology at The Christie NHS Foundation Trust. "There’s a strong rationale for the evaluation of weekly dose paclitaxel after settling into the first line of treatment," Clamp said, adding that preclinical animal evidence demonstrated improved drug delivery, increased tumor cell apoptosis, and reduced angiogenesis with metronomic taxane treatment.

ICON8 (NCT01654146) included 1566 patients with epithelial ovarian cancer who had FIGO stage IcG3-IV disease. Participants were randomized 1:1:1 to 3 arms:

- arm 1, standard chemotherapy: carboplatin area under the curve (AUC)5/6 plus paclitaxel 175 mg/m² every 3 weeks (n = 522),
- arm 2, weekly paclitaxel: carboplatin AUC5/6 every 3 weeks plus paclitaxel 80 mg/m² once weekly (n = 523), or
- arm 3, weekly carboplatin-paclitaxel: carboplatin AUC2 plus paclitaxel 80 mg/m² once weekly (n = 521).

In updated PFS analysis, the median PFS was 17.4 months in arm 1, 20.1 months in arm 2, and 20.1 months in arm 3. No statistically significant difference was observed in either arm 2 versus arm 1 (HR, 0.94; 97.5% CI, 0.80-1.10; P = .37) or arm 3 versus arm 1 (HR, 0.95; 97.5% CI, 0.81-1.11; P = .48). The restricted mean time to progression was 25.0, 25.5, and 25.9 months in arms 1, 2, and 3, respectively. "As with the primary analysis, there was evidence of nonproportional hazards in the survival curves, so the restricted mean survival time is the most appropriate primary estimate of treatment," Clamp said. "In fact, consistent with the primary analysis, there was no difference in restricted mean survival time across all 3 treatment arms."

At the time of the final database lock on April 3, 2020, there were 319 deaths in arm 1 (61%), 300 deaths in arm 2 (57%), and 304 deaths in arm 3 (58%). The median OS was 47.4, 54.1, and 53.4 months in arms 1, 2, and 3, respectively. No significant improvement in OS was observed in arm 2 versus arm 1 (HR, 0.89; 97.5% CI, 0.74-1.06; P = .14) or arm 3 versus arm 1 (HR, 0.91; 97.5% CI, 0.76-1.09; P = .27; TABLE).

"[Although] the hazard ratio in arm 2 is in favor of 3-weekly carboplatin and weekly paclitaxel compared [with] standard treatment and the [hazard ratio of] 0.91 [favors] weekly carboplatin and weekly paclitaxel...the confidence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Arm 1: standard 3-weekly: carboplatin AUC 5 + 175 mg/m² paclitaxel (n=522)</th>
<th>Arm 2: weekly paclitaxel: carboplatin AUC 5 + 80 mg/m² paclitaxel (n=523)</th>
<th>Arm 3: weekly carboplatin-paclitaxel: carboplatin AUC 2 + paclitaxel 80 mg/m² (n=521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>47.4</td>
<td>54.1</td>
<td>53.4</td>
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<tr>
<td>Log-rank P value vs arm 1</td>
<td>N/A</td>
<td>.14</td>
<td>.27</td>
</tr>
<tr>
<td>HR vs arm 1 (97.5% CI)</td>
<td>N/A</td>
<td>0.89 (0.74-1.06)</td>
<td>0.91 (0.76-1.09)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>17.4</td>
<td>20.1</td>
<td>20.1</td>
</tr>
<tr>
<td>Log-rank P value vs arm 1</td>
<td>N/A</td>
<td>.37</td>
<td>.48</td>
</tr>
<tr>
<td>HR vs arm 1 (97.5% CI)</td>
<td>N/A</td>
<td>0.94 (0.80-1.10)</td>
<td>0.95 (0.81-1.11)</td>
</tr>
<tr>
<td>Restricted mean TTP, months</td>
<td>25.0</td>
<td>25.5</td>
<td>25.9</td>
</tr>
</tbody>
</table>

AUC; area under curve; N/A, not available; OS, overall survival; PFS, progression-free survival; TTP, time to progression.
Frontline Nivolumab/Chemo Combo Improves Survival in Gastric Cancers

by JESSICA HERGERT

FIRST-LINE TREATMENT WITH the combination of nivolumab (Opdivo) and chemotherapy led to a statistically significant survival benefit among previously untreated patients with PD-L1-positive advanced gastric cancer, gastroesophageal junction (GEJ) cancer, or esophageal adenocarcinoma versus chemotherapy alone, according to findings from the phase 3 CheckMate 649 (NCT02872116) study presented during the European Society for Medical Oncology Virtual Congress 2020.

At a minimum follow-up of 12.0 months, the median overall survival (OS) was 14.4 months with nivolumab plus chemotherapy (95% CI, 13.1-16.2) versus 11.1 months with chemotherapy alone (95% CI, 10.0-12.1) in patients with a PD-L1 combined positive score (CPS) of 5 or greater (HR, 0.71; 98.4% CI, 0.59-0.86; P < .0001), translating to a 29% reduction in the risk of death with the combination.

Additionally, in this population, the combination led to a 32% reduction in the risk of disease progression or death compared with chemotherapy alone (HR, 0.68; 98% CI, 0.56-0.81; P < .0001). Specifically, the median progression-free survival (PFS) was 7.7 months (95% CI, 7.0-9.2) versus 6.0 months (95% CI, 5.6-6.9), respectively.

“I believe that nivolumab plus chemotherapy will represent a new potential standard first-line treatment for patients with advanced gastric cancer, gastroesophageal junction [cancer], or esophageal adenocarcinoma,” said Markus Moehler, MD, PhD, lead study author and head of gastrointestinal oncology at the Mainz University Clinic in Germany, during a presentation of the data. “There was a statistically significant and clinically meaningful overall survival benefit in patients whose tumors expressed PD-L1 CPS 5 or higher, [as well as] CPS 1 or higher, and in all randomized patients.”

In the trial, 1581 patients were randomized 1:1 to receive nivolumab 360 mg plus capcitabine (Xeloda) and oxaliplatin (Eloxatin) every 3 weeks or nivolumab 240 mg plus leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX) every 2 weeks (n = 789) versus capcitabine and oxaliplatin or FOLFOX alone (n = 792). A total of 60% of patients had a PD-L1 CPS of 5 or greater.

OS and PFS in patients with CPS of 5 or greater served as dual primary end points of the trial (TABLE). Secondary end points consisted of OS in all randomized patients and those with a PD-L1 CPS of 1 or greater, as well as PFS and overall response rate (ORR).

In patients with a PD-L1 CPS of 1 or greater, the median OS was 14.0 months with the combination (95% CI, 12.6-15) versus 11.3 months with chemotherapy alone (95% CI, 10.6-12.3; HR, 0.77; 99.3% CI, 0.64-0.92; P < .0001). The median PFS for this patient population was 7.5 months (95% CI, 7.0-8.4) compared with 6.9 months (95% CI, 6.1-7.0), respectively (HR, 0.74; 95% CI, 0.65-0.85).

“Further hypothesis-generating analyses are under way in our DPS cohort to determine if there is a subgroup of patients who may benefit [from] the [denser] approach,” Clamp said.

No changes in the toxicity profiles of the weekly regimens were observed when compared with results presented at prior meetings. Any grade 3/4 adverse events (AEs) were reported in 42% of patients treated in arm 1 compared with 62% and 53% in arms 2 and 3, respectively. Predefined notable AEs included grade 2 or higher sensory neuropathy (28% vs 24% vs 23%), grade 2 anemia (26% vs 52% vs 36%), grade 3/4 anemia (5% vs 13% vs 5%), and grade 3/4 febrile neutropenia (4% vs 6% vs 3%).

“[Arms 2 and 3] were associated with an increased incidence of any grade 3 or 4 events during treatment, but this was predominantly driven by uncomplicated grade 3 or 4 neutropenia,” Clamp said.

“Reassuringly, incidence of febrile neutropenia was low in all 3 treatment arms, and we did not see any increase in the incidence of grade 2 neuropathy in the 2 dose-dense paclitaxel-containing regimen.”

These data showed that the dose-dense regimen did not show improved survival results, and therefore the 3-weekly carboplatin-paclitaxel regimen remains the standard of care chemotherapy component for the first-line treatment of patients with ovarian cancer, Clamp concluded.

REFERENCE

intervals cross unity, and so there is no statistically significant improvement in overall survival,” Clamp explained.

Baseline characteristics were well balanced among the arms. The median age of study participants was 62 years; 72% had serous histology; 10.5% had stage IC-IIA disease; 18% had stage IIA-IIIB disease; and 71% had stage IIIIC-IV disease.

Half (50%) of patients planned delayed primary surgery (DPS) or were considered inoperable and 48% had immediate primary surgery (IPS). In a subgroup analysis, patients in the DPS cohort treated in arms 2 and 3 experienced a longer median overall survival (39 and 37 months, respectively) compared with those in arm 1 (32 months). However, no statistically significant improvement in overall survival was observed with the dose-dense regimen in either setting.

“At a minimum follow-up of 12.0 months, the median overall survival with nivolumab plus chemotherapy alone (95% CI, 10.0-12.1) in patients with a PD-L1 combined positive score (CPS) of 5 or greater (HR, 0.71; 98.4% CI, 0.59-0.86; P < .0001), translating to a 29% reduction in the risk of death with the combination.

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REFERENCE
Among all randomized patients, the median OS was 13.8 months (95% CI, 12.6-14.6) versus 11.6 months (95% CI, 10.9-12.5), respectively (HR, 0.80; 98% CI, 0.68-0.94; P = .0002). Further, the combination led to a 33% reduction in the risk of disease progression or death for this population. The median PFS was 7.7 months (95% CI, 7.1-8.5) with nivolumab and chemotherapy versus 6.9 months (95% CI, 6.6-7.1) with chemotherapy alone (HR, 0.77; 95% CI, 0.68-0.87).

compared with 45% (95% CI, 40%-50%), respectively. In detail, the best reported responses were complete response (12% vs 7%, respectively), partial response (48% vs 38%), stable disease (28% vs 34%), and progressive disease (7% vs 11%).

The median duration of response was 9.5 months (95% CI, 8.0-11.4) with the combination versus 7.0 months (95% CI, 5.7-7.9) with chemotherapy alone. The median time to response for this patient population was 1.5 months for both regimens.

Regarding safety, nivolumab plus chemotherapy elicited an expected toxicity profile, and no new safety signals were reported. Among all patients, any-grade treatment-related adverse effects (TRAEs) occurred in 94% of patients treated with nivolumab plus chemotherapy versus 89% of patients treated with chemotherapy alone. Grade 3 or 4 TRAEs were observed in 59% and 44% of patients, respectively. The most common any-grade TRAEs (≥ 25%) across both arms were nausea, diarrhea, and peripheral neuropathy.

Additionally, 36% of patients discontinued the combination because of TRAEs versus 24% of patients treated with chemotherapy alone. In the combination arm, 12 patients died as a result of treatment-related toxicity compared with 4 patients in the chemotherapy-alone arm.

“Overall the safety signals for the combination were consistent for the known safety signals for the individual drugs [in the regimen].”

—MARKUS MOEHLER, MD, PhD

The overall survival, according to prespecified subgroups [including] region, ECOG [status], and others, consistently favored the combination of nivolumab plus chemotherapy,” Moehler said. Of note, in 880 patients from the overall population stratified for microsatellite instability (MSI) status, 34 patients were identified as having MSI-high disease. The median OS was not reached in those treated with the combination versus 8.8 months with chemotherapy alone (unstratified HR for death, 0.33).

Investigators noted that the ORR was not formally tested, but data demonstrated that response and duration of response in patients with target lesion measurements at baseline also favored the combination versus chemotherapy alone and were more durable. The ORR for patients with CPS of 5 or greater was 60% (95% CI, 55%-65%)

An additional arm of the study evaluating the combination of nivolumab plus ipilimumab (Yervoy) will be reported at an upcoming medical meeting.

REFERENCE

More on ESMO 2020

Our broadcast features live virtual interviews with thought leaders analyzing key studies presented at the ESMO Virtual Congress 2020. Robert L. Coleman, MD, a 2020 Giants of Cancer Care® award winner, gives his take on noteworthy research in gynecologic cancers; Shilpa Gupta, MD, of Cleveland Clinic, and Scott T. Tagawa, MD, MS, of Weill Cornell Medicine, discuss genitourinary cancers; Stephen V. Liu, MD, of Georgetown Lombardi Comprehensive Cancer Center, talks about lung cancer; Priyanka Sharma, MD, of the University of Kansas School of Medicine delves into breast cancer; and Yelena Y. Janjigian, MD, of Memorial Sloan Kettering Cancer Center, details gastrointestinal cancer findings.


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TABLE. Primary End Points CheckMate 649

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPS ≥ 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab plus chemotherapy (n = 473)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>14.4 (HR, 0.71; 98.4% CI, 0.59-0.86; P &lt; .0001)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.7 (HR, 0.68; 98% CI, 0.56-0.81; P &lt; .0001)</td>
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<tr>
<td></td>
<td>Chemotherapy (n = 482)</td>
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<tr>
<td>Median OS, months</td>
<td>11.1</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>6.0</td>
</tr>
</tbody>
</table>

CPS, combined positive score; OS, overall survival; PFS, progression-free survival.
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Tipifarnib Shows Potential in HRAS-Mutant Head and Neck Cancers

by DENISE MYSHKO

ALTHOUGH THE ROLE OF HRAS mutations in a range of cancers was discovered more than 40 years ago,1 targeting the alterations has proved challenging. Now, investigators are testing tipifarnib, a novel drug that inhibits a critical enzyme needed for HRAS activation,2 in patients with head and neck squamous cell carcinoma (HNSCC) whose tumors harbor the mutation.

The AIM-HN/SEQ-HN trial (KO-TIP-007; NCT03719690) is an ongoing registrational, phase 2 study assessing the objective response rate (ORR) of tipifarnib in patients with incurable HRAS-mutant HNSCC. The international study was launched after tipifarnib demonstrated signs of efficacy in this patient population during a basket trial, according to Alan L. Ho, MD, PhD, a leading investigator of the drug.

“We were testing tipifarnib in HRAS [mutation-positive tumors] in several malignancies and found this particularly intriguing signal in HRAS patients with head and neck cancer,” Ho said in an interview with OncologyLive®. “Broadly speaking for head and neck cancer, it has been an exciting time for treatment for these patients with the advent of immunotherapy. But for patients with recurrent or metastatic disease, this is still an incurable disease and one where there is still a huge need for therapeutics,” said Ho, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, New York.

Investigators are seeking to enroll 305 patients (80 HRAS-mutant HNSCC for AIM-HN and SEQ-HN; 225 HRAS with HNSCC for SEQ-HN), which is recruiting at 95 locations in the United States, Europe, Australia, and Asia Pacific nations. The study has 2 cohorts: AIM-HN (n = 80), including 59 with high variant allele frequency (VAF) HRAS mutations and 21 with low VAF HRAS mutations, and SEQ-HN (n = 225). In AIM-HN, patients with HRAS-mutant HNSCC will receive tipifarnib monotherapy twice a day orally at 600 mg on days 1 to 7 and days 15 to 21 of 28-day treatment cycles.

The primary end point is the ORR in high VAF HRAS-mutant HNSCC. Secondary end points are ORR among HRAS-mutant HNSCC of any VAF, duration of response (DOR), time to response, and progression-free survival (PFS), as well as safety/tolerability, effects of tipifarnib on quality of life, and time to progression. SEQ-HN is a parallel prospective observation cohort that will compare treatment outcomes with first-line systemic therapy and other demographic/clinical characteristics in patients with HRAS-mutant HNSCC who enrolled in AIM-HN and a matched control set of patients with HRAS wild-type tumors (FIGURE).2,3

MECHANISM OF ACTION
Tipifarnib is a small molecule inhibitor of farnesyltransferase, an enzyme involved in the posttranslational modification of the RAS family proteins, which include HRAS, NRAS, and KRAS.4 Dysregulated activity of this signaling network has been implicated in various cancers, including head and neck squamous cell carcinoma. Tipifarnib inhibits the posttranslational modification of RAS family proteins by blocking the farnesylation process, which is critical for the activation and signaling of these proteins. By inhibiting farnesylation, tipifarnib prevents the proper folding and membrane localization of RAS proteins, leading to their degradation and thereby inhibiting their downstream signaling pathways. This mechanism of action has shown promise in the treatment of HRAS-mutant head and neck cancers, as evidenced by the ongoing AIM-HN and SEQ-HN trials.
in approximately 30% of human cancers. In HNSCCs, HRAS is mutated in approximately 6% of tumors and is overexpressed in 30%, Ho said during a presentation at the 2020 American Society of Clinical Oncology Virtual Scientific Program.

These mutations also are found in 2% of lung squamous cell carcinoma and 5% of urothelial carcinoma, whereas overexpression in those cancer types is 8% and 25%, respectively.

During the past 20 years, investigators have sought to develop farnesyltransferase inhibitors (FTIs) for RAS-mutant cancers, Ho said.

“It was based on the understanding that all RAS isoforms including mutant RAS required localization to the membrane in order to activate its downstream signaling and to promote oncogenesis,” he said.

“The idea was if you could inhibit that enzyme, you could delocalize RAS from the membrane and extinguish its signaling, and that would be a way to kill these RAS-mutant tumors.”

Although FTIs exhibited promise in preclinical studies, data from phase 2 and 3 trials showed modest outcomes. Ho said it was later discovered that other mechanisms come into play that maintain RAS localization in the membrane. HRAS mutations, he said, may be more susceptible to FTIs.

Tipifarnib is an FTI initially studied extensively in the late 1990s and early 2000s but did not achieve response rates robust enough to support registration studies. More than 5000 patients have been treated with tipifarnib, and although the agent has demonstrated responses in several tumor types, its mechanisms of action were not well understood.

Since then, the use of next-generation sequencing has been able to identify specific driver mutations in patient populations. Tipifarnib is currently the only FTI under investigation for HRAS-dependent HNSCC, according to Kura Oncology, the company developing the drug.

**RECENT EARLY-PHASE FINDINGS**

The rationale for testing tipifarnib in HRAS-mutant HNSCC stems from findings from the phase 2 KO-TIP-001 trial (NCT02383927) that evaluated the agent in patients with solid tumors with a mutation.

For the head and neck cohort, HRAS positivity was defined as a missense mutation with a VAF of 20% or greater and serum albumin of 3.5 g/dL or greater or HRAS VAF of 35% or greater.

In 18 evaluable patients, treatment with tipifarnib resulted in a 50.0% ORR (95% CI, 26.0%-74.0%) with a median DOR of 14.7 months (95% CI, 2.1-not reported). The median PFS was 5.9 months (95% CI, 3.5-19.2), and median OS was 15.4 months (95% CI, 7.0-46.4).

In a cohort of 12 evaluable patients with recurrent, metastatic HRAS-mutant salivary gland cancer, 1 patient achieved a partial response with tipifarnib therapy (8.3%) and 7 reached stable disease (58.3%).

In addition to HNSCC, tipifarnib was studied in a phase 2 trial (NCT02535650) in patients with previously treated, metastatic urothelial cancer with missense HRAS mutations or STK11 single nucleotide variant.

The ORR in 21 patients who received tipifarnib therapy was 24% (95% CI, 6%-42%); no response was observed in patients with wild-type HRAS tumors.

The median PFS was 4.7 months (95% CI, 2.5-5.6), and median OS was 6.1 months (95% CI, 5.0-7.2).

The most frequently observed adverse effects included fatigue (86%), anemia (76%), and neutropenia (67%).

**FUTURE DIRECTIONS**

The FDA has approved fast track designations for tipifarnib in HRAS-mutant HNSCC and adult patients with relapsed or refractory T-cell lymphomas including angioimmunoblastic T-cell lymphoma (AITL), follicular T-cell lymphoma, and nodal peripheral T-cell lymphoma with T follicular helper phenotype. Clinical data reported at the 2019 American Society of Hematology Annual Meeting showed durable activity from tipifarnib as a monotherapy in relapsed or refractory AITL in an ongoing single-arm phase 2 study (KO-TIP-002; NCT02464228). The ORR was 50% (95% CI, 28%-72%) in 20 evaluable patients with AITL and 70% (95% CI, 36%-93%) in 10 patients with KIR-mutated AIT.

**REFERENCES**


Introducing DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes¹

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 reaction (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.
DARZALEX®: For a strong start to their treatment journey

~3 to 5 minute administration

• Subcutaneous injection is substantially faster than intravenous daratumumab. The recommended dose of DARZALEX® is 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously over ~3 to 5 minutes. DARZALEX® is for subcutaneous use only. Do not administer intravenously.1

See the Dosage and Administration section of the Prescribing Information for dosing considerations and dosing schedules for approved regimens.

See Important Safety Information below for hypersensitivity and administration reactions, pre-medication and post-medication requirements, and other important considerations for use of DARZALEX®.

Get the latest data and information at darzalexhcp.com/faspro

Contact your Oncology Specialist to learn more about DARZALEX®

Efficacy consistent with intravenous daratumumab

• DARZALEX® demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients:1
  – ORR was 41% (95% CI: 35%, 47%) for DARZALEX® (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259)1
  – Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent1

  • In a single arm of a multicohort, open-label trial, DARZALEX® with lenalidomide and dexamethasone (DRd) was evaluated in 65 patients with multiple myeloma who had received ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%)1
  • In a single arm of a multicohort, open-label trial, DARZALEX® with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%)1

Fewer systemic ARRs vs intravenous daratumumab

• Nearly 3x reduction in systemic administration-related reactions (ARRs) with DARZALEX® vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZALEX® had a systemic ARR of any grade vs 34% with intravenous daratumumab).1

• Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX®. See Important Safety Information for more details.

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® until recovery of neutrophils. In lower body weight patients receiving DARZALEX®, 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® until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® can cause fetal harm when administered to a pregnant woman. DARZALEX® 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® and for 3 months after the last dose.

The combination of DARZALEX® 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®. Type and screen patients prior to starting DARZALEX®.

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®-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The most common adverse reaction (≥20%) with DARZALEX® 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 hematologic laboratory abnormalities (≥40%) with DARZALEX® are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.


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**INFORMATION AND USAGE**

**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.

**CONTRAINDICATIONS**

**DARZALEX FASPRO** is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase-fihj or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity and Other Administration Reactions**

Both systemic administration-related reactions and local injection-site reactions can occur with **DARZALEX FASPRO**.

**Systemic Reactions**

In a pooled safety population of 400 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, pruritus, chills, vomiting, nausea, and hypotension.

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 reaction (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 (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: 9 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 **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 (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.

**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 (see Use in Specific Populations). 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 (see References). The determination of a patient's ABO and Rh type are not impacted (see Drug Interactions). Notify blood transfusion centers of this interference with serological testing and inform blood banks [see Drug Interactions].

**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 (see Drug Interactions). 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 following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
- Neutropenia [see Warning and Precautions].
- Thrombocytopenia [see Warning and Precautions].

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
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/50,000 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.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, musculoskeletal and connective tissue disorders, constipation, pyrexia, pneumonia, and dyspnea. Dosage interruptions due to an adverse reaction occurred in 5% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia and hypercalcemia.

The most common adverse reaction (≥20%) was upper respiratory tract infection. Neutropenia was the most common hematological adverse reaction (≥20%). Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure. Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

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

Table 3 summarizes the adverse reactions 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 Bortezomib, Melphalan and Prednisonea</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades ≥3 (%)</td>
</tr>
<tr>
<td>Decreased leucocytes</td>
<td>98</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>88</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>58</td>
</tr>
</tbody>
</table>

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

### 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>All Grades (%)</td>
<td>Grades ≥3 (%)</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>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>Urinary tract infection</td>
<td>11</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
</tr>
<tr>
<td></td>
<td>Track pain</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
</tr>
</tbody>
</table>

- Fatigue includes asthenia, and fatigue.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
- Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
- Bronchitis includes bronchitis, and bronchitis viral.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Cough includes cough, and productive cough.
- Only grade 3 adverse reactions occurred.

### Adverse Reactions in COLUMBA

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

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/50,000 units administered subcutaneously or daratumumab 18 mg/kg administered intravenously; each administered 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. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure. Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

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

Table 4 summarizes the adverse reactions 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>All Grades (%)</td>
<td>Grades ≥3 (%)</td>
</tr>
<tr>
<td>Decreased leucocytes</td>
<td>94</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</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>

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

### 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=258)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>8</td>
</tr>
</tbody>
</table>

- 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.
- Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.
- Fatigue includes asthenia, and fatigue.
- Infusion reactions includes terms determined by investigators to be related to infusion.
- Cough includes cough, and productive cough.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Only grade 3 adverse reactions occurred.
- Grade 5 adverse reactions occurred.

Clinically 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, hypercalcemia, dehydration
- Psychiatric disorders: insomnia
- Vascular disorders: hypertension
- Nervous system disorders: dizziness, peripheral 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
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO® (N=192)</th>
<th>Intravenous Daratumumab (N=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leucocytes</td>
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<td>19</td>
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<td>14</td>
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<tr>
<td></td>
<td>39</td>
<td>16</td>
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</tbody>
</table>

Denominator is based on the safety population treated with DARZALEX FASPRO® (N=260) and Intravenous Daratumumab (N=256).

Immunogenicity

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

Treatment-emergent anti-daratumumab antibodies were detected 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 had limitations in detecting anti-daratumumab antibodies in the presence of the high titers of antibodies or the combination of DARZALEX FASPRO® and lenalidomide. Treatment-emergent anti-HuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO® as monotherapy and in 8% (18/192) of patients who received DARZALEX FASPRO® as part of a combination therapy. The anti-HuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-HuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience

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

Immune System: Anaphylactic reaction

Gastrointestinal: Pancreatitis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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 reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assays may occur in patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO®-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is 2% to 4% and 15% to 20%, respectively. There is no available data on the use of DARZALEX FASPRO in pregnant women treated with lenalidomide and hyaluronidase-fihj injection.

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO® is administered with lenalidomide and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO®. Refer to lenalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Maternal and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [See Use In Specific Populations].

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, refer to the lenalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO® and for 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO® as monotherapy and for at least 3 months after the last dose. Additionally, refer to the lenalidomide prescribing information for additional information.

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of a systemic administration-related reaction: Itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [See Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [See Warnings and Precautions].

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding [See Warnings and Precautions].

Embryo-Fetal Toxicity

Advises 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].

Advises females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO® and for at least 3 months after the last dose [See Use In Specific Populations].

Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements [see Use In Specific Populations].

Advise patients to use effective contraception during treatment with DARZALEX FASPRO® and for 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

Advise males to use effective contraception during treatment with DARZALEX FASPRO® and for at least 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

Advises patients to inform their healthcare provider of a known or suspected pregnancy [See Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Inform patients that DARZALEX FASPRO can affect the results of some tests used to determine infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [See Warnings and Precautions].

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [See Warnings and Precautions].

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [See Warnings and Precautions].

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Hamid Highlights Emerging Biomarkers for Immunotherapy in Melanoma

by HAYLEY VIRGIL

**Where has efficacy been observed with biomarkers in melanoma?**

When you talk about biomarkers, you’re looking at any evidence that can help you monitor disease status, whether it’s recurrence in the adjuvant setting or the presence of progressive disease in the metastatic setting. They can also be predictive [and inform treatment] before [a patient] starts their therapy; [there are] predictive biomarkers of response and for toxicities.

It’s hoped that they will help us understand which therapies to choose, where to go, and what to avoid—whether it’s giving a therapy that would [pose] a significant risk of a life-threatening toxicity despite response, or indicating no chance of response or even a high chance of response. If we have a regimen that has a 30% response rate, by using predictive biomarkers to select a better subset of patients [to receive it], we can offer them a 70% response rate. We can potentially prevent patients from wasting 3 months of their time on a treatment [that won’t work]. We can offer patients the ability to move forward and do better.

**How has TMB helped to guide immunotherapy decisions for patients with this disease?**

TMB has [played] a significant [role in identifying] patients who would respond to immunotherapy, not just in melanoma. High TMB has been used to [predict] response to immunotherapy; that has been well known for CTLA-4 and PD-1 agents. Multiple [studies have indicated] that.

We know that TMB for PD-L1 responses is important, ergo the FDA’s recent approval of pembrolizumab for patients who have high TMB. It is an indicator of a patient who is going to have a higher response rate to treatment.

**How is ctDNA being used to predict response in this patient population?**

Melanoma Institute Australia has done many studies looking at ctDNA. We know that the majority of melanomas have ctDNA, [and] not just 50% of patients who have BRAF mutations but for the other mutations that exist as well. We know that it’s a good marker for risk of relapse in the adjuvant setting. If [a patient] has ctDNA, they get their sentinel node incision, and [if their ctDNA] goes down to 0, they will have a lower risk of relapse than someone who has persistent ctDNA.

In addition, [ctDNA] has been used as an indicator for response. One abstract that was recently presented looked at patients who had pseudoprogression, [and investigators] used ctDNA to help understand what that means. At 12 weeks, when you image and it looks as if the patient’s disease has grown, you don’t know whether it has grown and is shrinking now or is consistently [growing]. Some investigators have correlated that with ctDNA. As you get to week 12, if ctDNA has decreased, that’s a greater indication that what you’re seeing is a late response; that tells you that you can hold on longer and reevaluate in 4 to 6 weeks.

We know that ctDNA can help [us] understand what’s going on in the body or in the adjuvant setting. However, most recently, investigators from Melanoma Institute Australia looked to see whether we can understand what’s going on with patients who have brain metastases [by using ctDNA]. Unfortunately, it does not [help in that instance]. ctDNA is not quite standard, not quite ready for prime time, but it’s coming. It’s involved in almost every clinical trial right now to understand what’s going on.

**What is the emerging role of mRNA in immunotherapy?**

mRNAs have been reported in multiple...
SKIN CANCERS

Clinical Perspectives

Cancers; they’re regulators of gene expression and can be correlated with certain genes that are invariably expressed in certain malignancies. Their quantification can help us in the same way as potential biomarkers to diagnose early lesions or early metastatic disease—[that is,] what’s there when we initially see the tumor and whether it recurs.

In addition, they can help with understanding therapeutic targets. If mRNAs are associated with therapeutic pathways that we can target, then we can understand how to use them as therapeutic targets.

[mRNAs and ctDNAs] can potentially help you in multiple ways. They can help you initially by understanding whether there is a target. If there is [detection of a BRAF mutation in] ctDNA, [identified] with a blood test, you may have an earlier way of knowing whether a tumor has that mutation and [be able to] target it. As we get more and more savvy with understanding mRNAs and what happens with the changes and the evolution of the tumor, we may be able to understand newer targets and how to introduce either combinatorial therapeutics or even a whole new therapeutic landscape for a patient.

If something shows up as a patient is progressing and it’s a pathway that we know how to target, then we understand the molecular events that are ongoing in that tumor without having to biopsy. In addition, hopefully, it can help us to understand prognosis. In situations where we don’t know where the tumor is coming from, we can look at gene signatures and ctDNA and those tumors of unknown primary, and we can potentially adequately treat.

Are any other emerging biomarkers under examination right now that you feel are particularly interesting?

Let’s talk about the adjuvant space. Right now, PD-1 is getting more and more of a foothold in adjuvant therapy. Jeffrey S. Weber, MD, PhD, of NYU Langone Health, [presented] updated data from the CheckMate 238 trial [NCT02388906], which examined ipilimumab (Yervoy) versus nivolumab (Opdivo) in the adjuvant setting; this set nivolumab as the standard. With the updated analysis, [investigators] examined exploratory biomarkers at baseline and median values, [which in turn] help us understand who can benefit more from these therapies. [Specifically,] they looked at IFNγ gene expression profile.

What [the CheckMate 238 investigators] found was that improved relapse-free survival [RFS] was seen with higher IFNγ expression with both nivolumab and ipilimumab, a higher CD8 T-cell infiltration, high TMB, and lower peripheral myeloid-derived stem cells. When you put those together—higher TMB and IFNγ—that gave the best RFS. This allows us to understand how to then use those biomarkers going forward to help with not just RFS but also long-term survival.

In the future, we can understand not only how [these markers] can [potentially] help us [choose] the right therapy for a whole group of patients but also that there’s a [possible] subgroup of patients who do better with [certain agents]. We don’t know [the answer to] that yet, but we can [use this to] understand which adjuvant therapy to choose, whether it’s looking at the unknown question of whether we should target BRAF or use PD-1 in the adjuvant setting for a patient with BRAF-mutated disease.

What is future biomarker research going to focus on?

A lot of information on biomarkers of toxicity was presented during the 2020 ASCO [American Society of Clinical Oncology] Virtual Scientific Program; I believe that is where we are going next. What are these biomarkers that can help us understand toxicity? In one study, investigators examined autoantibodies as predictors for survival and immune-related adverse effects [AEs] in checkpoint inhibition therapy.²

Investigators examined samples and data analyses, [including] pretreatment samples from checkpoint inhibitor–treated stage IV melanoma. [They profiled] 832 autoantibody antigens and [examined] patients treated with [several different agents prior to baseline]. They looked at these data analyses and identified antigens and associated pathways that lead to toxicities.

[Anti]-MIF antibodies showed increased disease progression and a lower risk of immune-related AEs. [Anti]-FGFR1 antibodies were associated with progressive disease, shorter survival, and a lower rate of immune-related AEs. [Anti]-MAGE B4 antibodies were associated with better survival and a higher rate of immune-related AEs. [Anti]-MITF antibodies were associated with colitis.²

In the future, you [will see] this idea that has been brought forth in many sci-fi novels: With 1 drop of blood, we can look at antibodies, ctDNA, and gene signatures. In a multivariate analysis, this can tell us how [a patient is] going to respond on different treatments. That’s where we’re going in the next 3 to 5 years. Not just understanding initially but [grasping] dynamic changes within the tumor, tumor microenvironment, and tumor expression through mRNA, changes in ctDNA, etc, to understand what is going on.

It doesn’t have to be just pathological, like a biopsy or blood. We’re also looking at predictors of response through imaging. There are now PET [positron emission tomography] tracers that target T cells, and we’re using that as a dynamic predictive marker for response. There are companies that are doing studies trying to understand what that means. With an initial CD8 T-cell scan, you can tell where your CD8s are. Then, after a couple of doses, you can image and see whether you’re really trafficking those CD8 T cells into the tumor.

This is an easy read: If you see it getting hot where the tumors are, you’re getting your desired effect. If not, you’re not getting your desired effect and may need to add something or move on to [a different treatment]. You may need to go directly to targeted therapies. Ultimately, these can help us understand what is happening with our patients.

REFERENCES


STARTING IN JULY 2021, the Centers for Medicare & Medicaid Services (CMS) will roll out a new model for reimbursing radiation oncologists for treating patients based on bundled payments rather than the current fee-for-service system, a change that is setting off alarm bells among providers. Practices and cancer centers in randomly selected zip codes will be required to participate in the new radiation oncology (RO) Model, which is expected to cover approximately 30% of eligible Medicare fee-for-service care episodes.¹,²

Originally slated to begin January 1, 2021, the model was delayed based on feedback from stakeholders, CMS announced on October 21.

The model is structured as a way to test whether the bundled payment approach can reduce Medicare costs for radiation therapy (RT) while maintaining or improving quality of care for beneficiaries.³

The current fee-for-service reimbursement system is based on the number of treatments that patients receive and the care setting in which RT is offered, giving providers and suppliers an incentive to schedule therapy over more visits and favor one type of site over another, CMS said in announcing the RO Model.¹ CMS estimates that the RO Model will save Medicare $230 million over 5 years.¹

Radiation oncologists are bracing for a decrease in reimbursements.

“This is going to involve a significant cut in pay for me and my practice. I am confident it will be a very difficult program for me to participate in,” said David C. Beyer, MD, medical director of radiation oncology of Cancer Centers of Northern Arizona Healthcare in Sedona, said in an interview with OncologyLive.⁴

The implications for practices required to participate in the model are dire, particularly in light of the ongoing pandemic and required practices to make significant practice changes to comply with the January 1, 2021, implementation date,” Adler said in an email before the CMS announced it was delaying implementation. “Financially, the RO Model will bring more pain to practices. According to the final rule, the RO Model will cut payments to group practices by 6% and hospital outpatient departments by 4.7%. Amazingly, these cuts are deeper than what CMS estimated in its proposed rule.”

The agency unveiled the new system on September 18, 2020, as part of a final rule on specialty care models, capping discussions about episode-based payment approaches that began in 2014.² The model will be tested over a 5-year period.³

Although radiation oncologists had an opportunity to weigh in on proposed changes, the final rule fails to address many of the key concerns they raised, Theodore L. DeWeese, MD, chair of the ASTRO Board of Directors, said in a statement.⁵ DeWeese is also vice president for interdisciplinary patient care for Johns Hopkins Medicine, the Kimmel Professor of Radiation Oncology and Molecular Radiation Sciences, and director of the Department of Radiation Oncology and Molecular Radiation Sciences at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

“The rule fails to accept the overwhelming majority of good faith recommendations provided by ASTRO, radiation oncology stakeholders, patients, and Congress,” Adler said. Constantine A. Mantz, MD, chief policy
officer for 21st Century Oncology in Florida and vice-chair of ASTRO’s Health Policy Council, said ASTRO and other stakeholder groups in radiation oncology had devoted an unprecedented amount of time to engage with the Center for Medicare & Medicaid Innovation in a good faith effort to help develop a payment model that would realize savings and quality improvements while providing stable payments to sustain physician practices.

“The final rule does not meet the goals of reducing the administrative burden for the physician or providing stable reimbursement to support high-quality RT services across all practice settings and geographies,” Mantz said. “I hope that we will have an opportunity to redress the model’s most critical faults.”

DETAILS OF THE NEW MODEL
Under the current fee-for-service structure, Medicare pays providers for each individual RT service they perform, and that payment can differ depending on where the patient received care, such as a hospital outpatient department, physician group practice, or freestanding radiation therapy center.

In 2017, the US Department of Health & Human Services identified 3 key reasons for changing the system: the lack of site neutrality for payments, incentives that encourage volume of services over the value of services, and coding and payment challenges. The RO Model provides bundled payments for a 90-day “episode” of care for 16 cancer types: anal cancer, bladder cancer, bone metastases, breast cancer, cervical cancer, central nervous system tumors, colorectal cancer, head and neck cancer, liver cancer, lung cancer, lymphoma, pancreatic cancer, prostate cancer, upper gastrointestinal cancer, and uterine cancer.

The proposal originally included 40% of radiation oncology episodes, Trevor J. Royce, MD, MPH, said in an interview. “It is still quite high and higher than some of the [other] alternative payment models that have come out,” he said.

The University of North Carolina (UNC) at Chapel Hill, where Royce is an assistant professor in the Department of Radiation Oncology, has been selected to participate in the program.

“We like to practice evidence-based medicine, and the highest level of evidence comes from randomized controlled trials,” said Royce, who is immediate past vice-chair of ASTRO’s Association of Residents in Radiation Oncology Executive Committee.

“CMS needed enough participants to make sure this policy experiment was powered enough to see if there are savings being generated by the model.”

Adler said bundled payments could represent an opportunity to improve care and lower costs.

“Buried deep within the pile of the RO Model’s complex payment methodology, layers of mandated cuts, and burdensome requirements, there is a foundation for a sound episodic-payment model that incentivizes better care, instead of more care. Unfortunately, CMS has undermined the potential and promise of the model with unnecessary cuts and requirements that threaten its potential, along with the viability of required practices,” Adler said.

HOW PAYMENTS ARE STRUCTURED
The reimbursement structure of the RO Model is complex, with much of the methodology driven by historical performance of the practice or institution. Adjustments are made for case mix, outside trends, and geographic location, as well as any withholding for performance on quality elements and incorrect payments.

Episode payments are split into 2 components: a professional component (PC) payment, which is the payment to the physician, and the technical component (TC) payment, which is the payment for the equipment, supplies, personnel, and costs related to RT services.

<table>
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<th>FIGURE. Key Features of New Radiation Oncology Model</th>
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<tr>
<td><strong>Bundled payment system</strong></td>
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<td><strong>Site neutrality</strong></td>
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<td><strong>Cancer types</strong></td>
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CMS also applies a “discount” and withholds for errors, quality, and patient experience. The discount factor is the percentage that CMS reduces an episode payment. The discount factor for the provider is 3.75%, and the discount factor for the technical component is 4.75%. Practices can earn back some funds withheld for quality and patient experience based on clinical data and quality measure reporting.

“Practices receive half of their payment when treatment is initiated and the other half at the end of treatment; however, there is a lengthy period of reconciliation to resolve the withhold,” Adler said.

Mantz said the most striking positive feature of the model is its 1-payment-per-cancer-type methodology, which frees the physician from making clinical decisions that are in part tied to reimbursement and instead encourages decisions that are more oriented to the best care of the patient.
“By issuing the same payment per cancer type, reimbursement is decoupled from the quantity and type of prescribed services. The physician, therefore, is incentivized to make the best clinical and cost-effective treatment decision for the patient. Ideally, the end result of such a model is a win-win-win scenario for patient, provider, and payer,” Mantz said.

CMS will assess participants’ performance on measures of quality and patient experience and tie those assessments to payment. The rule requires participants to submit key clinical data that can be used for additional research, improvements to pricing, and the development of new quality measures specific to radiation oncology.

The RO Model qualifies as an Advanced Alternative Payment Model (APM) and a Merit-based Incentive Payment System (MIPS) APM under the Quality Payment Program. These are existing CMS programs that tie payments to quality and cost-efficient care. Practices that participate in the APM program must meet the RO Model requirements to receive incentive payments under the APM.

The RO Model assesses 4 quality measures: plan of care for pain, treatment summary communication, preventive care and screening for depression, and advanced care plan. Additionally, patients are to be given the Consumer Assessment of Healthcare Providers and Systems survey.

IMPACT ON RADIATION ONCOLOGISTS

One of the biggest issues surrounding the RO Model is related to implementation. Participants will likely need a new technology infrastructure for coding and billing procedures, as well as a way to integrate that data into the electronic health record (EHR) to capture the required quality data.

CMS estimates that implementation costs related to the model would be less than $2000 in the first year and less than $1000 in subsequent years. But Mantz says this underestimates the needed modifications in billing and collections processes and likely EHR-related costs to comply with the model’s quality reporting requirements. “I would anticipate significant related costs for any size practice to adapt to these new requirements,” he said.

Beyer predicted this will likely cost his practice $10,000 to implement, in addition to his time.

“If MIPS was any indication, this will be 30 to 40 hours of my time where I am not seeing patients and I’m not reading articles to keep my skills up.”

Adler pointed out that payment rates won’t be available until December 2020, and then practices have to compare those rates with past payments to budget for 2021. “Some practices expect they will need to hire new staff to implement the complex new requirements, despite experiencing layoffs, hiring freezes, and financial strains due to COVID-19,” he said.

Another complicating factor, Royce said, involves large hospital networks that cover multiple zip codes or have clinics in different areas.

“It is still not entirely clear how that will play out if part of the health care system is included in the bundle and part of it is not,” he said. “UNC is one example of that.”

For a full list of references, see the article at OncLive.com.
Stage Is Set for Continued Progress in the Melanoma Clinic

by MARK R. ALBERTINI, MD

UNPRECEDENTED TREATMENT ADVANCES HAVE been made during the last decade for patients with advanced melanoma. These strides are especially impressive when contrasted with the limited treatment options available for similar patients before 2011. At that time, standard-of-care treatment considerations for patients with advanced melanoma were limited to chemotherapeutic agents that achieved transient responses without a confirmed survival benefit in small proportions of treated patients. Additionally, cytokine-based therapy with high-dose bolus interleukin-2 (IL-2) was available, and data showed an overall response rate of 16% and a 6% complete response rate in patients with metastatic melanoma. However, high-dose IL-2 has severe toxicity and was limited to patients with excellent performance status at specialized treatment centers. The treatment prioritization for metastatic melanoma at most academic medical centers was participation in an appropriate clinical trial. Unfortunately, conferred benefit remained infrequent until the successful translation of several insights from the lab to the clinic that changed the standard of care for patients with metastatic melanoma.

A WAVE OF CHANGE

One translational insight that improved outcomes for many patients with advanced melanoma was the identification of different genetic aberrations and genetic driver mutations—most prominently BRAF mutations—and the subsequent development of targeted agents that interfere with these pathways. This stimulated the development of BRAF and MEK inhibitors that improved the care of patients with BRAF-mutant metastatic melanoma by targeting the mitogen-activated protein kinase (MAPK) pathway. A second translational insight was the understanding that T cells can specifically recognize melanoma. Although this suggested an exciting therapeutic opportunity, an understanding of negative and positive T-cell costimulatory molecules was required to unleash T cells against melanoma and achieve effective antitumor responses first in preclinical models and then the clinic. This proved to be a game-changing insight for patients with melanoma and provided the foundation for several clinical studies that evaluated antitumor activity and explored underlying biological mechanisms.

The initial immune checkpoint inhibitor that improved survival for patients with metastatic melanoma was ipilimumab (Yervoy), an anti-CTLA-4 antibody. Since then, monoclonal antibodies that block PD-1 such as pembrolizumab (Keytruda) and nivolumab (Opdivo) improved outcomes with less toxicity than ipilimumab in metastatic melanoma. In addition, sustained long-term overall survival was seen in a greater percentage of patients with metastatic melanoma who received concurrent ipilimumab and nivolumab or nivolumab monotherapy than in those who received ipilimumab alone. However, treatment with combined immune checkpoint blockade has the consequence of more frequent and more severe immune-related adverse events.

FIGURE 1. Diagram of hu14.18-IL2

The genetically engineered fusion protein hu14.18-IL2 links interleukin-2 (IL-2) to the hu14.18 monoclonal antibody. Image courtesy of Paul M. Sondel, MD, PhD, adapted from Sondel PM, Hank JA. Cancer J Sci Am. 1997;3(suppl 1):S121-127.
CARBONE CANCER CENTER TAKES ACTION

The discovery of informative predictive biomarkers of response, as well as biomarkers of adverse events, is essential to guide patient care going forward. There is also tremendous enthusiasm to investigate combination treatments to enhance the antitumor activity that can be achieved with immune checkpoint blockade. Fortunately, we have a road map to guide us as we start our next journey.

A clinical trial (NCT03958383) at the University of Wisconsin Carbone Cancer Center in Madison is studying an intratumoral (IT) vaccine strategy with the GD2-reactive hu14.18-IL2 immunocytokine (IC) in patients with advanced (stage IV) or unresectable stage III melanoma who have disease progression after prior treatment with an FDA-approved therapy. The hu14.18-IL2 IC is a humanized monoclonal antibody (mAb) that is covalently linked to 2 molecules of IL-2 at the Fc region (FIGURE 1).12

How we got here

The hu14.18 mAb recognizes GD2, a disialo-ganglioside that is a cell membrane molecule predominantly found in tumors of neuroectodermal origin including melanoma, neuroblastoma, and certain sarcomas. GD2 is rarely found in normal tissues and mostly occurs in the cerebellum and peripheral nerves.12-14 Systemic administration of hu14.18-IL2 IC in patients with advanced melanoma was previously studied, with reported immune activation and reversible toxicities.15-16 Also reported was surgery to remove all identifiable melanoma either prior to or following the first of 3 courses of hu14.18-IL2 IC at 6 mg/m² on days 1, 2, and 3 of each 28-day course. We saw prolonged tumor-free survival in some patients at high risk for recurrence and death. Molecular markers associated with outcome also were identified.17-18

In preclinical testing in mice, the antitumor effects of hu14.18-IL2 were enhanced by administering hu14.18-IL2 directly into established GD2-positive tumors.19 In addition, a cooperative interaction between IT-IC, local radiotherapy (RT), and an anti-CTLA-4 antibody was demonstrated.20 A recent report suggested that this interaction may be multifactorial and that tumor-specific regulatory T (Tregs) cells harbored in untreated tumors may pose a challenge to the efficacy of in situ vaccination. Consequently, this led to the identification of potential therapeutic approaches to deplete local Tregs to circumvent this problem.21

What lies ahead

At Carbone Cancer Center, a phase 1/2 clinical trial has been opened to study the IT administration of hu14.18-IL2 with local radiation, nivolumab, and ipilimumab in patients with advanced melanoma (FIGURE 2). The study will include comprehensive correlative immune monitoring to translate this laboratory insight into the clinic.

The therapeutic goal is to convert the injected tumor into an effective in situ tumor vaccine, as has been shown in mice. The trial consists of 4 phases to study IT delivery of hu14.18-IL2 alone (phase 1a), in combination with local RT (phase 1b), in combination with local RT and systemic nivolumab (phase 1c), and in combination with local RT, systemic ipilimumab, and systemic nivolumab (phase 1d) in patients with advanced melanoma. The trial, which will evaluate safety, antitumor activity, and immunologic end points, is designed to replicate the striking antitumor responses this regimen achieved in preclinical models. Phase 1a of the trial is open, which involves IT delivery of hu14.18-IL2 alone.

The identification of effective treatments with curative potential for metastatic melanoma patients is the final destination of this melanoma roadmap. It is predicted that transformative insights in the lab will continue to guide the progress still needed for patients with metastatic melanoma.

MORE ON OncLive.com

O’Regan Recaps COVID-19 Changes

Ruth O’Regan, MD, describes protocols that the University of Wisconsin Carbone Cancer Center has put into place in light of the coronavirus disease 2019 (COVID-19) during an episode of the OncLive® On Air podcast. She discusses the rise of telemedicine, best practices for in-person visits in the clinic, and the importance of maintaining well visits throughout the pandemic. O’Regan is a professor and division head of Hematology and Oncology in the Department of Medicine at the University of Wisconsin School of Medicine and Public Health, and associate director of Clinical Research at Carbone.

LISTEN NOW: https://bit.ly/2FNPoDr
Important Safety Information

1L ES-SCLC
TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

PD-L1+ mTNBC
TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1(PD-L1-stained tumor-infiltrating immune cells (IC) of any intensity covering ≥1% of the tumor area), as determined by an FDA-approved test.

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

mTNBC=metastatic triple-negative breast cancer.

Important Safety Information

Serious Adverse Reactions
Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

• **Immune-mediated pneumonitis.** Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, have occurred. Permanently discontinue TECENTRIQ for Grade 3 or 4 pneumonitis

• **Immune-mediated hepatitis.** Immune-mediated hepatitis and liver test abnormalities, including fatal cases, have occurred. Permanently discontinue TECENTRIQ for AST or ALT elevations more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal

• **Immune-mediated colitis.** Immune-mediated diarrhea or colitis have occurred. Permanently discontinue TECENTRIQ for Grade 4 diarrhea or colitis

• **Immune-mediated endocrinopathies.** Thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, including diabetic ketoacidosis, and hypophysitis/hypopituitarism have occurred

• **Other immune-mediated adverse reactions.** TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. Permanently discontinue TECENTRIQ for Grade 4 immune-mediated adverse reactions involving a major organ system.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer V.2.2019.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2019.

References:
TECENTRIQ: THE COMMON THREAD IN IMPORTANT ADVANCEMENTS FOR LUNG AND BREAST CANCER TREATMENT

1L ES-SCLC

TECENTRIQ + carbo/etop
The first FDA-approved treatment for 1L ES-SCLC in 20 years¹,²

PD-L1+ mTNBC

TECENTRIQ + nab-pac
The first FDA-approved cancer immunotherapy combination in PD-L1+ mTNBC¹

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend atezolizumab (TECENTRIQ) in combination with nab-paclitaxel as a preferred option for patients with PD-L1 positive recurrent or metastatic triple-negative breast cancer (Category 2A)⁴

Infections. Severe infections, including fatal cases, have occurred

Infusion-related reactions. Severe or life-threatening infusion-related reactions have occurred. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion-related reactions

Embryo-fetal toxicity. TECENTRIQ can cause fetal harm in pregnant women. Verify pregnancy status prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

Most Common Adverse Reactions

The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ in combination with other antineoplastic drugs for NSCLC and SCLC were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%), and decreased appetite (27%).

The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ with paclitaxel protein-bound for mTNBC were alopecia (56%), peripheral neuropathies (47%), fatigue (47%), nausea (46%), diarrhea (33%), anemia (28%), constipation (25%), cough (25%), headache (23%), neutropenia (21%), vomiting (20%), and decreased appetite (20%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages.

This indication is approved under accelerated approval based on tumor response rate and durability of response in patients with metastatic urothelial carcinoma who:

1.1 Urothelial Carcinoma verification and description of clinical benefit in a confirmatory trial(s).

• TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC
• TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

In clinical studies enrolling 2421 patients who received TECENTRIQ as a single-agent, adenocarcinoma occurred in 11% of patients, including Grades 3-4 in 0.3% of patients. 2.2% of the 2421 patients received the use of hormone replacement therapy. Hypothyroidism and thyrotoxicosis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Type 1 Diabetes Mellitus Monitor patients for hyperglycemia or other signs and symptoms of diabetes.

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman.
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 data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 201 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single-arm studies (PCD4989g, IMvigor210, BIRCH, FRI) which enrolled 324 patients with metastatic urothelial carcinoma, 16,36 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2016 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 26% were exposed for longer than 12 months. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 10% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%).

In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in 2421 patients with NSCLC (N = 2229) or SCLC (N = 192) enrolled in five randomized, active-controlled trials, including IMpower150 and IMpower133. Among the 2021 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 26% were exposed to TECENTRIQ for longer than 12 months. Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with other antineoplastic drugs, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (49%), nausea (38%), allopurinol (34%), constipation (29%), diarrhea (28%) and decreased appetite (27%). The data described below in this section were obtained from one open-label, single-arm, multi-cohort study (IMvigor210) and three randomized open-label, active-controlled studies (OAK, IMpower150 and IMpower133). In these trials, TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks. This section also describes data from one randomized, placebo-controlled study (IMpower130) in which TECENTRIQ was administered at a dose of 480 mg intravenously every 2 weeks in combination with paclitaxel protein-bound to 412 patients with metastatic TNBC.

Urothelial Carcinoma

Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 1), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were treated with TECENTRIQ at a dose of 1200 mg intravenously every 3 weeks. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks). Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ, the most common Grade 3–4 laboratory abnormalities in ≥ 1% of patients were hyperbilirubinemia (3%), hyperkalemia (3%), increased alkaline phosphatase (3%), creatinine increase (2%), and lymphopenia (2%).

Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure. TECENTRIQ was discontinued for adverse reactions in 4% of patients. The adverse reactions leading to discontinuation were diarrhea (1.7%), fatigue (0.8%), hyperkalemia (0.8%), and dyspnea (0.8%). Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were hypothermia (1.7%), fatigue (1.7%), and creatinine increase (1.7%). Adverse reactions leading to discontinuation occurred in 31% of patients; the most common (≥ 1%) were hypothermia (1.7%), fatigue (1.7%), and creatinine increase (1.7%).

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (≥ 2%) were urinary tract infection, hematologic, acute kidney injury, intestinal obstruction, pyrexia, venous thrombosis/embolism, sepsis, and pneumonia. Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction. TECENTRIQ was discontinued for adverse reactions in 3% of patients. Sepsis led to discontinuation in 0.6% of patients.

Adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure. TECENTRIQ was discontinued for adverse reactions in 4% of patients. The adverse reactions leading to discontinuation were diarrhea (1.7%), fatigue (0.8%), hyperkalemia (0.8%), and dyspnea (0.8%). Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were hypothermia (1.7%), fatigue (1.7%), and creatinine increase (1.7%). Adverse reactions leading to discontinuation occurred in 31% of patients; the most common (≥ 1%) were hypothermia (1.7%), fatigue (1.7%), and creatinine increase (1.7%).

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (≥ 2%) were urinary tract infection, hematologic, acute kidney injury, intestinal obstruction, pyrexia, venous thrombosis/embolism, sepsis, and pneumonia. Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction. TECENTRIQ was discontinued for adverse reactions in 3% of patients. Sepsis led to discontinuation in 0.6% of patients.

Table 2: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>TECENTRIQ N = 119</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue¹</td>
<td>52</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema²</td>
<td>17</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea³</td>
<td>24</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain⁴</td>
<td>15</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite⁵</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Neurological and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>18</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Rash⁶</td>
<td>17</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection⁷</td>
<td>17</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough⁸</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea⁹</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

¹ Includes fatigue, asthenia, lethargy, and malaise
² Includes edema peripher, scrotal edema, lymphedema, and edema
³ Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
⁴ Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
⁵ Includes decreased appetite and early satiety
⁶ Includes rash, dermatitis, dermatitis acneform, rash maculopapular, rash erythematous, rash pruritic, rash macular, and rash papular
⁷ Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urethritis
⁸ Includes cough and productive cough
⁹ Includes dyspnea and exertional dyspnea

Table 3: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>15</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>10</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>7</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>5</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4</td>
</tr>
<tr>
<td>Increased AST</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>3</td>
</tr>
<tr>
<td>Hematology</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>TECENTRIQ N = 310</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>18</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>22</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>14</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Meeting International, randomized, open-label trial in which 393 chemotherapy-naive patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.2)]. The median duration of exposure to TECENTRIQ was 6.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

The most common Grades 3–4 adverse reactions (≥2%) in patients receiving TECENTRIQ were fatigue, anemia, hypertension, febrile neutropenia, diarrhea, pneumonia, nausea, decreased appetite, dyspnea, and pulmonary embolism.

Serious adverse reactions occurred in 44% of patients. The most frequent serious adverse reactions (≥2%) were febrile neutropenia, pneumonia, diarrhea, and hypertension.

TECENTRIQ was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonia (1.8%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, bronchocytopenia, fatigue, allergic reaction, anemia, pneumonia, pyrexia, hypophosphatemia, febrile neutropenia, increased ALT, dyspnea, dehydration, and proteinuria. All reactions leading to discontinuation of TECENTRIQ were grade 3 or 4.

The most common Grade 3–4 adverse reactions (≥2%) were pneumonia, sepsis, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure.

The most common Grades 3–4 adverse reactions (≥2%) were pneumonia, sepsis, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure. Adverse reactions leading to discontinuation of TECENTRIQ were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (>1%) were pneumonia, fever, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see Clinical Studies (14.2)]. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression or clinical progression or docetaxel [578] mg/m² intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 66% former smoker, 16% current smoker, and 65% had ECOG performance status of 1. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

Adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 16% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure. Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (>1%) were pneumonia, fever, function test abnormality, dyspnea, fatigue, pyrexia, and back pain. Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in OAK.

Table 6: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>10</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>4</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>5</td>
</tr>
<tr>
<td>Increased AST</td>
<td>1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Increased AST</td>
<td>52</td>
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<tr>
<td>Hypomagnesemia</td>
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<td>Hypocalcemia</td>
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</tr>
<tr>
<td>Hypoproteinuria</td>
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<td>Hyponatremia</td>
<td>52</td>
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<tr>
<td>Increased Alkaline Phosphate</td>
<td>52</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>42</td>
</tr>
<tr>
<td>Increased AST</td>
<td>40</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>30</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>28</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>28</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>26</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
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<td>Hypocalcemia</td>
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<tr>
<td>Hypoproteinuria</td>
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<td>Hyponatremia</td>
<td>23</td>
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<td>19</td>
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<td>Hyperkalemia</td>
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</tr>
<tr>
<td>Increased Creatinine</td>
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</tr>
<tr>
<td>Hypocalcemia</td>
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<td>Hypophosphatemia</td>
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<td>Hypocalcemia</td>
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<tr>
<td>Hypoproteinuria</td>
<td>16</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>15</td>
</tr>
<tr>
<td>Increased AST</td>
<td>13</td>
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<tr>
<td>Increased TSH</td>
<td>12</td>
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<tr>
<td>Hyperkalemia</td>
<td>12</td>
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<tr>
<td>Increased Creatinine</td>
<td>12</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>12</td>
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<tr>
<td>Hypophosphatemia</td>
<td>12</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>12</td>
</tr>
<tr>
<td>Hypoproteinuria</td>
<td>12</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>9</td>
</tr>
<tr>
<td>Increased AST</td>
<td>8</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>8</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>8</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>8</td>
</tr>
<tr>
<td>Hypocalcemia</td>
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<td>8</td>
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<td>Hypocalcemia</td>
<td>8</td>
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<td>Hypoproteinuria</td>
<td>8</td>
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<tr>
<td>Hyponatremia</td>
<td>7</td>
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<tr>
<td>Increased AST</td>
<td>7</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>7</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>7</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>7</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>7</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>7</td>
</tr>
<tr>
<td>Hypoproteinuria</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 9: Laboratory Abnormalities Worsening From Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in OAK

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>37.3</td>
<td>17.9</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>48.8</td>
<td>30.3</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>46.5</td>
<td>28.8</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>88.0</td>
<td>51.9</td>
</tr>
<tr>
<td>Increased ASAT</td>
<td>33.2</td>
<td>18.1</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>28.7</td>
<td>15.8</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>9.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Decreased Creatinine</td>
<td>22.5</td>
<td>16.2</td>
</tr>
</tbody>
</table>

1 Graded according to NCI CTCAE version 4.0

2 Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy

Table 10: Adverse Reactions Occurring in ≥20% of Patients Treated with TECENTRIQ and paclitaxel protein-bound. Table 11 summarizes selected laboratory abnormalities worsening from baseline that occurred in at least 20% of patients in the TECENTRIQ treated patients.

Table 11: Laboratory Abnormalities Worsening From Baseline Occurring in ≥20% of Patients with TNBC (IMpassion130)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ in combination with paclitaxel protein-bound (n=452)</th>
<th>Placebo in combination with paclitaxel protein-bound (n=438)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>46.7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>69.3</td>
<td>39.7</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>88.3</td>
<td>57.1</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>2.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Decreased Creatinine</td>
<td>21.3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

2 Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy
Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

### Table 12: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ with Carboplatin and Etoposide</th>
<th>Placebo with Carboplatin and Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>General</td>
<td>N = 198</td>
<td>N = 196</td>
</tr>
<tr>
<td>Fatigue/asthma</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td>Decreased appetite</td>
<td>27</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

### Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Carboplatin and Etoposide</th>
<th>Placebo with Carboplatin and Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td>N = 198</td>
<td>N = 196</td>
</tr>
<tr>
<td>Anemia</td>
<td>94</td>
<td>17</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>73</td>
<td>45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>Chemistry</td>
<td>N = 198</td>
<td>N = 196</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Decreased TSH</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Increased liver Creatinine</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Hyperphosphatasaemia</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>21</td>
<td>NA</td>
</tr>
</tbody>
</table>

1 Graded per NCI CTCAE v4.0

### 8. USE IN SPECIFIC POPULATIONS

#### 8.7 Pregnancy

**Risk Summary**

Based on its mechanism of action (see Clinical Pharmacology (12.3)), TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death (see Data). Advise females of reproductive potential of the potential risk to a fetus.

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

**Data**

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

#### 8.2 Lactation

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human milk is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

#### 8.3 Females and Males of Reproductive Potential

**Pregnancy Testing**

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ (see Use in Specific Populations (8.7)).

**Contraception**

Females

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.7)). Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment (see Nonclinical Toxicology (13.5)).

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

Of 2481 patients with urothelial carcinoma, lung cancer, and triple-negative breast cancer who were treated with TECENTRIQ in clinical studies, 45% were 65 years and over and 11% were 75 years and over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older, and younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Immune-Mediated Adverse Reactions**

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment or discontinuation or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath (see Warnings and Precautions (5.5)).
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of the abdomen, lethargy, or easy bruising or bleeding (see Warnings and Precautions (5.4)).
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in the stool, or severe abdominal pain (see Warnings and Precautions (5.3)).
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, hyperparathyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis (see Warnings and Precautions (5.5)).
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions (see Warnings and Precautions (5.5)).

**Infections**

Advise patients to contact their healthcare provider immediately for signs or symptoms of infection (see Warnings and Precautions (5.6)).

**Embryo-Fetal Toxicity**

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions (5.6)). Use in Specific Populations (8.7, 8.8). Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ (see Use in Specific Populations (8.8)).

**Lactation**

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose (see Use in Specific Populations (8.8)).
Uncovering TP53 Mutations in MDS, AML Requires NGS

by RACHEL NAROZNIAK, MA

TP53-TARGETED TREATMENT OPTIONS represent an unmet need for patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). However, identifying the mutation, which presents in 8% to 12% and 5% to 10% of MDS and AML cases, respectively, by next-generation sequencing (NGS) remains an important component of shaping a patient’s treatment course, according to David Sallman, MD.

“People could argue that there is no therapy specifically approved for TP53-mutant disease. If they are going to give any patient with high-risk MDS a hypomethylating agent [HMA] such as azacitidine, then they don’t think that sequencing necessarily matters, but it does have prognostic implications,” said Sallman, an assistant member in the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida, in an interview with OncologyLive®.

“Median overall survival for patients with high-risk, TP53-mutant MDS and AML is less than 1 year. That’s significantly worse than all other subtypes,” Sallman added.

HMA therapy is the standard of care for patients with high-risk MDS; however, TP53-mutant disease treated with HMAs infrequently achieves durable clonal suppression and typically has poor overall survival (OS). The efficacy of standard treatment is commensurately lacking in AML. Moreover, TP53 mutations are known to not only confer resistance to cytotoxic chemotherapy but also correlate with poor responses to induction chemotherapy in MDS and AML. The complete response rate for TP53-mutant, induction chemotherapy-treated AML spans 20% to 40% with high relapse rates; median OS ranges from 4 to 9 months.

Beyond HMAs and chemotherapy, TP53 alterations also complicate the pursuit of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Across de novo MDS and therapy-related MDS, TP53 is the only somatic gene mutation to predict not only inferior OS but also suboptimal benefit from allo-HSCT. Poor long-term outcomes seen with allo-HSCT in TP53-affected AML have discouraged the execution of the process in this patient subgroup, with 2 studies demonstrating early relapse, with posttransplant relapse rates of 50% and 40% at 100 days and 6 months after allo-HSCT, respectively.

“The presence of a TP53 mutation has significant impact in the consideration of a clinical trial,” Sallman said. “Patients who have a TP53 mutation and are getting standard treatment are likely not going to do very well, and so they really need to see if there is any alternative option that can be considered. We strongly recommend clinical trials given the poor outcomes to standard therapy.”

Although Sallman maintains that it is “really important to get the sequencing result before making treatment decisions,” he acknowledges that the amount of time required to receive NGS results can be an obstacle to therapeutic expeditiousness. “Whereas an NGS platform at an academic center typically can turn around results between approximately 4 and 10 days, commercial labs can sometimes take 2 to 3 weeks. So, I think trying to identify these patients quickly can be a challenge. Some of these patients have severe cytopenias and do require quite urgent therapy,” Sallman explained.

TESTING FOR TP53 MUTATIONS

The National Comprehensive Cancer Network (NCCN) “highly recommends” genetic testing for somatic mutations in genes associated with MDS and in AML. The NCCN also advises that all patients with AML should be tested not only for TP53 alterations, but also for c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1/2, RUNX1, and ASXL1 on the basis that these mutations are “associated with specific prognoses in...”
The inconsistent application of NGS is a current challenge in the TP53-mutant MDS and AML landscapes, but Sallman is optimistic that ongoing efforts to develop targeted therapies for this population will galvanize greater uptake of the modality. “I think, as more drugs with a molecular focus get approved, NGS is going to become a standard. We saw it happen when FLT3 and IDH1 [biomarkers] and 2 inhibitors were approved in AML. Then testing for all of those aberrations became standard in what felt like overnight. So, I think it’s really the treatment option that informs the identification of mutations,” Sallman said.

In settings where NGS for MDS and AML is not frequently performed, health care providers should be aware of the clinical indicators that could suggest TP53-mutant disease and subsequently guide a patient to sequencing. “We have observed in patients with excess blast MDS with high ringed sideroblasts a strong correlation with TP53 mutations,” Sallman explained. Cytogenetic abnormalities can also signal TP53-mutant disease. Aberrations in chromosomes 5, 7, and 17 are also “highly concordant with the presence of a TP53 mutation and can be observed [via a fluorescence in situ hybridization panel], which can be turned around in about 1 to 2 days,” he added.

High numbers of blasts or ringed sideroblasts or cytogenetic abnormalities are not surrogate markers for diagnoses of TP53-mutant disease based on NGS results. These findings are clinical cues that the patient could belong to this molecularly specific subset of the MDS and AML population. Given the prognostic and therapeutic implications of a TP53 mutation, providers should not only be aware of the predictors of TP53 alterations, but also actively look for them when patients present with MDS or AML, Sallman concluded.

REFERENCES
NRG1 Fusions Hold Promise as Pan-tumor Target

by JANE DE LARTIGUE, PhD

THE IDENTIFICATION OF chromosomal rearrangements that result in oncogenic gene fusions ushered in the era of molecularly targeted therapies in oncology, beginning with the groundbreaking approval of imatinib (Gleevec) in 2001. This “magic bullet” targets the BCR-ABL1 gene fusion protein in patients with chronic myeloid leukemia.1

Thanks to the development of advanced sequencing technologies, a multitude of cancer-driving gene fusions have since been identified, prompting the development of a growing number of novel therapeutic options directed at such alterations. These agents include additional FDA-approved drugs that inhibit BCR-ABL protein activity as well as therapies aimed at ALK, RET, NTRK, and FGFR2 fusions.1,2

Investigators are seeking to add fusions involving the NRG1 gene to the list of targets. First described in 2014 in lung adenocarcinoma, the most prevalent subtype of non–small cell lung cancer (NSCLC),3 NRG1 fusions have now been identified at low rates across many cancer types (FIGURE 1).4,5 Moreover, a growing body of evidence demonstrates that these fusions are oncogenic and potentially targetable in malignancies in desperate need of novel treatment options.6,7

NRG1 fusions activate the HER2-HER3 tyrosine kinase receptor pair, making it a potential target of interest in cancers associated with that pathway. The outcomes of preclinical studies have suggested that repurposing FDA-approved HER inhibitors, such as afatinib (Gilotrif), may be a highly attractive therapeutic strategy for NRG1 fusion–positive tumors. A growing number of case reports show clinical efficacy of afatinib in such tumors or suggest potential for investigational drugs targeting HER3.6,7

Prospective clinical trials, including multicenter basket studies, are under way for several of these drugs (TABLE). If successful, these studies could result in therapies directed at NRG1 fusions joining the growing global pipeline of tumor-agnostic therapies.

ACTIVATING THE PERFECT PAIR

The HER family (also called ERBB) is a group of 4 closely related cell-surface receptors that, when activated by their cognate ligands, trigger intracellular signaling pathways orchestrating vital cellular processes. Dysregulation of many of these processes leads to hallmarks of cancer.14,17

The NRG1 (or HRG1) gene encodes the neuregulin-1 (or heregulin) protein, the best-characterized member of a family of proteins that function as ligands for HER3 and HER4. NRG1 can be expressed as a number of different isoforms, all of which possess an epidermal growth factor (EGF)-like signaling domain through which they activate their receptors.6,7

Most NRG1 isoforms are transmembrane proteins, some of which undergo proteolytic processing to release a soluble version of the ligand. Thus, NRG1 can activate HER receptors on the same cell in which it is expressed (via autocrine signaling) and on neighboring or more distant cells (via paracrine signaling).6,7

Binding of their ligands triggers a conformational change in EGFR (also known as HER1), HER3, and HER4, exposing their dimerization domain. This allows these HER receptors to form a pair with a second HER receptor of either the same (homodimerization) or a different kind (heterodimerization). Dimerization triggers the intrinsic kinase activity of the

![FIGURE 1. NRG1 Fusions by Tumor Type](chart)
receptor and initiates intracellular signaling cascades (FIGURE 2). 6,7,18

Both HER2 and HER3 rely on heterodimerization for their activation, HER2 because it has no known activating ligand and HER3 because it has little or no intrinsic kinase activity compared with the other HER family members. 16,17

HER2 is the preferred dimerization partner for HER3,19 which contains multiple binding sites for the p85 regulatory subunit of the PI3K protein. Thus, HER2-HER3 heterodimerization is a key amplifier of PI3K/AKT signaling, in addition to a trigger for other signaling pathways, such as the MAPK pathway. 16,17

**A UNIQUE CANCER DRIVER**

In 2014, investigators identified a new type of genomic aberration in lung adenocarcinomas, in which the first 6 exons of the CD74 gene (containing its transmembrane domain, among other features) were fused to the exons of the NRG1 gene that encode its EGF-like receptor-binding domain.

The investigators went on to demonstrate that this gene fusion drives cancer development because the NRG1 EGF-like domain in the resulting fusion protein is overexpressed on the cell surface; this type of cancer is otherwise devoid of NRG1 expression. The NRG1 EGF-like domain functions as a ligand for HER3 and triggers HER2-HER3 heterodimerization and subsequent intracellular signaling via the PI3K/AKT pathway. 2,21

Up to that point, known drivers of lung cancer primarily involved alterations in tyrosine kinase receptors or downstream signaling kinases. NRG1 fusions represented a unique mechanism of oncogenesis, whereby signaling through a tyrosine kinase receptor was affected indirectly through aberrant expression of its ligand.

Since that initial report, NRG1 fusions have been identified across a growing number of cancer types. To date, the largest analysis retrospectively examined more than 40,000 tumor specimens using comprehensive genomic profiling. 4

Across all tested samples, the incidence of NRG1 fusions was 0.2, but this varied among tumor types. More than half the fusions were identified in patients with NSCLC; however, just 0.3% of tested NSCLC specimens were fusion positive. NRG1 fusions were also identified in gallbladder, pancreatic, kidney, ovarian, breast, bladder, and colorectal cancers, as well as sarcomas. 4,5

A range of NRG1 fusion partners beyond CD74 have been identified, and they also vary among cancer types. In NSCLC, other fusion partners include the SDC4, SLC3A2, and ATP1B1 genes. In other malignancies, the genes SETD4, TSHZ2, and ZMYM2 (ovarian cancer); ADAM9 and COX10-ASI genes (breast cancer); and CDH1 and VTCN1 genes (pancreatic cancer) are among known fusion partners of NRG1. 5

Most NRG1 fusions described to date result in the formation of a chimeric protein that like CD74-NRG1, possesses an intact EGF-like domain from NRG1 and a transmembrane domain donated by the fusion partner. 11,12

NRG1 fusions have been shown to be associated predominantly with tumors with adenocarcinoma histology. In lung cancer, they appear to be particularly enriched in the invasive mucinous adenocarcinoma (IMA) subtype, a rare form of the malignancy that is associated with poor prognosis and rarely demonstrates currently targetable driver alterations, such as EGFR mutations or ALK fusions. 2,21

NRG1 fusions have largely been shown to be mutually exclusive with other oncogenic drivers across cancer types, although exceptions have been reported. Notably, in pancreatic ductal adenocarcinoma, NRG1 fusions are found predominantly in KRAS wild-type tumors and could offer a much-needed target for precision medicine in this notoriously therapeutically challenging tumor type. 5,11,12

The rarity of NRG1 fusions and the diversity of fusion partners may make detecting these fusions more challenging. Historically, fluorescence in situ hybridization and reverse transcriptase-polymerase chain

### TABLE. Ongoing Clinical Trials in NRG1 Fusion–Positive Tumors

<table>
<thead>
<tr>
<th>Agent (industry developer)</th>
<th>Mechanism of action</th>
<th>Clinical setting</th>
<th>Target enrollment</th>
<th>Phase/trial name (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>Pan HER inhibitor</td>
<td>NRG1-rearranged locally advanced and metastatic tumors</td>
<td>60</td>
<td>Phase 2 NCT/DKTK PMO-1604 (NCT04410653)*</td>
</tr>
<tr>
<td>(Boehringer Ingelheim)</td>
<td></td>
<td>Wild-type tumors</td>
<td>NA</td>
<td>Phase 2 TAPUR (NCT02693535)*</td>
</tr>
<tr>
<td>Tarloxotinib (Rain Therapeutics)</td>
<td>EGFR/HER2 inhibitor activated by hypoxia</td>
<td>Solid tumors with NRG1 or ERBB family gene fusions</td>
<td>60</td>
<td>Phase 2 RAIN (NCT03805841)</td>
</tr>
<tr>
<td>Seribantumab (Elevation Oncology)</td>
<td>HER3-directed monoclonal antibody</td>
<td>Locally advanced or metastatic solid tumors with NRG1 gene fusion</td>
<td>75</td>
<td>Phase 2 CRESTONE (NCT04383210)</td>
</tr>
<tr>
<td>Zenocutuzumab (MCLA-128) (Merus)</td>
<td>HER2/HER3 dual-targeting monoclonal antibody</td>
<td>NSCLC, pancreatic cancer, other solid tumors with NRG1 fusion</td>
<td>250</td>
<td>Phase 1/2 eNRGy (NCT02912949)</td>
</tr>
</tbody>
</table>

NA, not available; NSCLC, non–small cell lung cancer.
*Trial is not yet recruiting.
*Basket trial.
Cancer in cells, 

Afatinib may be more suppressing growth of NRG1 fusion–driven EGFR-mutated NSCLC. Although EGFR approved for the treatment of patients with afatinib, a pan-HER inhibitor that is already prospective trials. have propelled several drugs into ongoing generating even greater enthusiasm and with activity of HER-targeted drugs in patients prospective studies demonstrating clinical activity of HER-targeted drugs in patients with NRG1 fusion–positive tumors are generating even greater enthusiasm and have propelled several drugs into ongoing prospective trials.

The largest body of evidence exists for afatinib, a pan-HER inhibitor that is already approved for the treatment of patients with EGFR-mutated NSCLC. Although EGFR inhibition was relatively ineffective at suppressing growth of NRG1 fusion–driven cancer in cells,4 afatinib may be more successful because it targets other HER family members in addition to EGFR and thus blocks the major mechanism of NRG1-driven oncogenesis, which is through HER2/HER3 signaling.

A number of published case reports describe patients with NRG1 fusion–positive lung adenocarcinoma who responded to afatinib.9,10,14 Responses have also been noted in patients with other types of solid tumors, including cholangiocarcinoma and pancreatic cancer.10-12

**MULTIPLE PATHS TO CLINICAL ACTIONABILITY**

Because NRG1 fusions drive cancer through HER receptors and downstream signaling pathways, HER-targeted agents make attractive therapies for patients whose tumors harbor these fusions. Preclinical studies have demonstrated activity in NRG1 fusion–positive cancer cell lines and durable tumor regression in patient-derived xenograft models for a number of HER family–targeted drugs.

Furthermore, case reports and small retrospective studies demonstrating clinical activity of HER-targeted drugs in patients with NRG1 fusion–positive tumors are generating even greater enthusiasm and have propelled several drugs into ongoing prospective trials.

The largest body of evidence exists for afatinib, a pan-HER inhibitor that is already approved for the treatment of patients with EGFR-mutated NSCLC. Although EGFR inhibition was relatively ineffective at suppressing growth of NRG1 fusion–driven cancer in cells,4 afatinib may be more successful because it targets other HER family members in addition to EGFR and thus blocks the major mechanism of NRG1-driven oncogenesis, which is through HER2/HER3 signaling.

A number of published case reports describe patients with NRG1 fusion–positive lung adenocarcinoma who responded to afatinib.9,10,14 Responses have also been noted in patients with other types of solid tumors, including cholangiocarcinoma and pancreatic cancer.10-12

**TARGETING HER3**

Because NRG1 is an activating ligand for HER3, NRG1 fusions could represent an alternative mechanism of HER3 pathway dysregulation in tumors that do not overexpress the receptor, which suggests a rationale for testing HER3-targeted antibodies in patients with these gene fusions.

Increased levels of HER3 expression have been noted across numerous cancer types and are associated with tumor development and resistance to a variety of anticancer therapies. For this reason, ongoing efforts to target HER3 have met with limited success, generally owing to insufficient efficacy.16,17,26

Merrimack Pharmaceuticals developed the HER3-targeted monoclonal antibody seribantumab (MM-121), and it was tested in randomized phase 2 clinical trials in NSCLC and ovarian and breast cancers.27-29 Seribantumab did not demonstrate significant clinical benefit in unselected patient populations, but the results of biomarker analyses suggested that a subset of patients with NRG1-expressing tumors derived benefit.27-29

However, in the phase 2 SHERLOC trial (NCT02387216), adding seribantumab to docetaxel in patients with previously treated NRG1-positive NSCLC failed to improve progression-free survival compared with docetaxel alone. NRG1 expression was assessed using immunohistochemistry...
(positive score, ≥ 1 +). Among 109 patients treated and available for assessment, the median progression-free survival for participants who received the seribantumab combination (n = 71) was 3.4 months (95% CI, 2.6-4.2) versus 4.1 months (95% CI, 2.8-6.3) for those who took docetaxel alone (n = 38), translating into an HR of 1.382 (95% CI, 0.813-2.350; P = .2302). The trial was subsequently terminated.20

In 2019, Elevation Oncology acquired seribantumab11 and is currently carrying out the phase 2 CRESTONE trial in patients with NRG1 gene fusions (NCT04383210). The study, which aims to enroll 75 patients, will identify NRG1 fusions through molecular assays on fresh or archived formalin-fixed paraffin-embedded tumor samples.

Meanwhile, several case reports suggest that HER3-targeted antibodies may have activity in patients with NRG1 fusions.

One patient with previously treated CD74-NRG1 fusion-positive IMA achieved a PR lasting more than 18 months when receiving GS2849330, an anti-HER3 antibody, during a phase 1 study (NCT01966445).4 Two patients with IMA harboring SLC3A2-NRG1 fusions were treated with erlotinib plus a different HER3-targeted antibody, lumretuzumab (RO5479599), and both achieved SD lasting nearly 4 months (NCT01482377).32

Dual targeting of both HER2 and HER3 may be more effective than blocking HER3 alone. Zenocutuzumab (MCLA-128) is a novel HER2/HER3-bispecific antibody described by developer Merus as having a dual “dock and block” mechanism of action. It binds to HER2 at a different epitope from that targeted by trastuzumab (Herceptin) and blocks the interactions between HER3 and both NRG1 and HER2.33,34

Zenocutuzumab was recently awarded orphan drug designation for the treatment of pancreatic cancer following signs of clinical activity in patients with this cancer type and NSCLC. In trial results reported at the 2019 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics international conference, 29 patients with NRG1 fusion-positive tumors across 8 cancer types were treated with zenocutuzumab at a dose of 750 mg every 2 weeks.

One patient with pancreatic adenocarcinoma with liver metastases achieved a PR, described as a reduction of cancer antigen (CA) 19-9 from 262 U/mL to 56 U/mL and a 44% reduction in tumor diameter. A second patient with pancreatic ductal adenocarcinoma with liver metastases achieved a reduction in CA 19-9 from 418 U/mL to 11 U/mL and a 22% reduction in tumor diameter. A patient with NSCLC and brain metastases who had progressed after 6 prior lines of therapy, including afatinib, experienced a PR, reported as a 33% reduction in tumor diameter and shrinkage of brain metastases.11 Zenocutuzumab is also being evaluated in the phase 1/2 eNRGyl trial in patients with advanced NRG1 fusion-positive solid tumors (NCT02912949).

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

For a full list of references, see the article at OneLive.com.
GAVRETO™—the only once-daily targeted RET therapy for patients with RET fusion+ metastatic NSCLC.¹

GAVRETO™ (pralsetinib) is indicated for the treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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

IMPORTANT SAFETY INFORMATION

Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of interstitial lung disease (ILD)/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased AST occurred in 69% of patients, including Grade 3/4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. Common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected) and increased alanine aminotransferase (ALT).

Avoid coadministration with strong CYP3A inhibitors. Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration cannot be avoided, increase the GAVRETO dose.

Please see Brief Summary of full Prescribing Information for GAVRETO on adjacent page.

INDICATIONS AND USAGE
GAVRETO™ (pralsetinib) capsules, for oral use. Initial U.S. approval: 2020
This indication is approved under accelerated approval.

DRUG INTERACTIONS

Avoid coadministration with strong CYP3A inhibitors.

DRUG METABOLISM

CYP3A: CYP3A decreases pralsetinib exposure, which may decrease the incidence and severity of adverse reactions of GAVRETO. Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily.

Adverse Reactions

The following adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic Events
- Risk of Impaired Wound Healing

Clinical Trials Experience

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

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET altered solid tumors in ARROW. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

RET Fusion-Positive Non-Small Cell Lung Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW. The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients: fatal adverse reaction which occurred in > 1 patient included pneumonia (n = 3) and sepsis (n = 2).
Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dose reductions in ≥2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

The most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected), and increased alanine aminotransferase (ALT).

Table 4 summarizes the adverse reactions in ARROW.

### Table 4: Adverse Reactions (≥15%) in Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue¹</td>
<td>35</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
</tr>
<tr>
<td>Edema²</td>
<td>20</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea³</td>
<td>24</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>16</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain⁴</td>
<td>32</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension⁵</td>
<td>28</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal</strong></td>
<td></td>
</tr>
<tr>
<td>Cough⁶</td>
<td>23</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia⁷</td>
<td>17</td>
</tr>
</tbody>
</table>

¹ Fatigue includes fatigue, asthenia
² Edema includes edema peripheral, face edema, periorbital edema, eyelid edema, edema generalized, swelling
³ Diarrhea includes diarrhea, colitis, enteritis
⁴ Musculoskeletal pain includes back pain, myalgia, arthralgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal stiffness, arthritis, spinal pain
⁵ Hypertension includes hypertension, blood pressure increased
⁶ Cough includes cough, productive cough, upper-airway cough syndrome
⁷ Pneumonia includes pneumonia, atypical pneumonia, lung infection, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal

*Only includes a Grade 3 adverse reaction

Table 5 summarizes the laboratory abnormalities in ARROW.

### Table 5: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>69</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>42</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>40</td>
</tr>
<tr>
<td>Increased calcium (corrected)</td>
<td>29</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>27</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>54</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>52</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 83 to 94 patients.

Clinically relevant laboratory abnormalities < 20% of patients who received GAVRETO included hyperphosphatemia (10%).

### DRUG INTERACTIONS

#### Effects of Other Drugs on GAVRETO

**Strong CYP3A Inhibitors**

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose.

**Strong CYP3A Inducers**

Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration cannot be avoided, increase the GAVRETO dose.
USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data
In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.5-2.2 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.5 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

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

Females and Males of Reproductive Potential
Based on animal data, GAVRETO can cause embryolethality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily.

Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to initiating GAVRETO.

Contraception
GAVRETO can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal contraceptives ineffective.

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

Infertility
Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility.

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

Animal Toxicity Data
In a 4-week repeat-dose toxicity study in non-human primates, physeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physeal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicity study, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Geriatric Use
Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

Hepatic Impairment
GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST).

Manufactured for: Blueprint Medicines Corporation, Cambridge, MA 02139, USA
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For more information, go to www.GAVRETO.com or call 1-888-258-7768.
Approximately 40% of patients with diffuse large B-cell lymphoma (DLBCL) experience refractory disease after initial treatment or have a relapse after achieving remission.1 Until the advent of chimeric antigen receptor (CAR) T-cell therapies, treatment options for these patients had been mostly palliative, especially for those ineligible for autologous stem-cell transplantation (ASCT) and those who relapsed after ASCT. Although CAR T-cell therapies have revolutionized the treatment landscape for relapsed/refractory (R/R) DLBCL, not all patients are candidates for this treatment. Of those who do receive it, 30% to 35% experience long-term benefit, demonstrating a great unmet need for others in the treatment landscape.

Emerging agents have started to shake up the R/R DLBCL armamentarium, but there is still a long road ahead to fully define their role. During an OncLive Peer Exchange®, a panel of lymphoma experts discussed several novel agents for R/R DLBCL, some of which have been recently approved. They examined the clinical trial data, discussed how these agents compare with CAR T-cell therapy, and provided insights on how they might be used in clinical practice. “Before long, we’ll need more sophistication in how we approach patients,” moderator John P. Leonard, MD, said. “Hopefully, that means we’ll be using treatments more effectively and have more tools at our disposal.”

Tafasitamab-cxix

Tafasitamab-cxix (Monjuvi) is a humanized anti-CD19 monoclonal antibody that has been mostly studied as a combination therapy, particularly with lenalidomide (Revlimid). On July 31, 2020, the FDA granted accelerated approval to the combination for adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, who are not eligible for ASCT.2

“The Fc portion has been enhanced to increase ADCC [antibody-dependent cell-mediated cytotoxicity] and ADCP [antibody-dependent cellular phagocytosis],” Kami J. Maddocks, MD, said. She noted that investigators initially examined tafasitamab in a single-arm study as monotherapy in patients with R/R non-Hodgkin lymphoma, the data from which demonstrated responses in DLBCL, including a few complete responses (CRs). In this phase 2a study (NCT01685008), investigators observed responses in 9 of the 35 patients (26%) with DLBCL (2 CRs and 7 partial responses [PRs]), with a median duration of response of 20.1 months (range, 1.1-26.5).3 “This study signaled that there might be some activity with this agent in large cell lymphoma,” Maddocks said. She proceeded to explain that the rationale for combining this agent with lenalidomide is that lenalidomide activates natural killer cells, thereby optimizing the tumor environment for tafasitamab.

Data from L-MIND (NCT02399085) provided the basis for the approval of tafasitamab in combination with lenalidomide. The phase 2, open label, multicenter, single-arm trial included 71 patients with DLBCL who received tafasitamab 12 mg/kg intravenously (days 1, 8, 15 and 22 of each 28-day cycle for 3 cycles, then days 1 and 15 only) with lenalidomide 25 mg orally (days 1-21) for a maximum of...
12 cycles, followed by biweekly tafasitamab as monotherapy. It was really targeted at those patients who relapsed after their initial therapy or maybe received a first salvage and then were not candidates for ASCT,” she said. All patients in the study had previously received 1 to 4 systemic regimens, at least 1 of which was an anti-CD20 therapy.4

Maddocks noted that the combination was well tolerated and that the adverse effects (AEs) were in line with expected AEs for lenalidomide monotherapy. The most common grade 3 or higher treatment-emergent AEs were hematologic abnormalities, including neutropenia (48%), thrombocytopenia (17%), and febrile neutropenia (12%).4 “There were very few infusion-related reactions. Approximately three-quarters of the patients were able to stay on lenalidomide 20 mg or higher,” Maddocks said.

**Tafasitamab/Lenalidomide vs CAR T-Cell Therapy**

The panelists proceeded to discuss tafasitamab plus lenalidomide in the context of CAR T-cell therapy and when it might be most useful. They noted that the patients in the L-MIND trial were not heavily pretreated, were not refractory to their first-line treatment, and did not have more aggressive disease subtypes, such as double- or triple-hit biology.

Subsequently, this population was different from those included in the CAR T-cell studies, such as ZUMA-1 (NCT02348216), JULIET (NCT02445248), and TRANSCEND-NHL-001 (NCT02631044), in which 77%, 54%, and 67% of patients, respectively, had primary refractoriness, and 69%, 51%, and 50% received more than 3 lines of therapy.3 Further, in reported data from the JULIET and TRANSCEND-NHL-001 studies, 27% and 22% of patients had double-hit lymphoma, respectively. “[CAR T-cell therapy] doesn’t care that you’re a double-hit. You can still respond and have durability. It’s the same thing if you’re primary refractory,” Matthew Lunning, DO, said. Thus far, there are no data to clarify whether this is also the case for tafasitamab plus lenalidomide.

It is also unknown whether tafasitamab plus lenalidomide can be used as a bridge to CAR T-cell therapy. National Comprehensive Cancer Network guidelines state, “It is unclear if tafasitamab will have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.”4 Lunning said that preclinical data have shown that there is no negative affect with tafasitamab. “[Cell line studies show] that it does engage the same CD19 antigen that you’d expect the CAR T cell to go after but, at least in cell lines, it did not appear to affect the CAR T cells,” he said. Maddocks added that there was 1 patient enrolled in the L-MIND trial who received CAR T-cell therapy after progression on tafasitamab plus lenalidomide and who has been in remission for more than a year. However, she warned that you cannot draw conclusions based on 1 patient. “As this combination becomes available to people, we’ll hopefully know more about whether there is an effect on the efficacy of CAR T,” she said.

Despite the unknown effect of tafasitamab plus lenalidomide as a bridging therapy to CAR T, the panelists agreed this may be a reasonable use. “If it takes a couple of weeks to get patients to their apheresis and then another 3 weeks to get them [to delivery], maybe tafasitamab is the best option. It’s 8 weekly doses early on and you’re getting drug exposure with the intent to go to CAR T-cell therapy or a patient could say no, and you haven’t lost anything if they’re responding,” Lunning said.

Lunning suspects tafasitamab plus lenalidomide will get a lot of use because “it is an IV [intravenous] therapy, given weekly for a lot of doses up front, and lenalidomide is an oral therapy that people are very comfortable using in lymphoma and multiple myeloma.” Subsequently, he emphasized the importance of capturing the data for those patients previously exposed to tafasitamab/lenalidomide who do not respond or who get a PR and go on to CAR T-cell therapy to determine the true durability of the combination. “That’s only going to come out with real-world experience data rather than a commercially funded experience,” Lunning said.

**SELENXOR**

The FDA granted selinexor (Xpovio) accelerated approval on June 22, 2020, as a single agent for adult patients with R/R DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.2 The oral agent represents a whole new class of drugs. “It’s unlike anything that we have for large cell lymphoma or any other cancers. It’s called a SINE [selective inhibitor of nuclear export] and it targets certain proteins that are exported out of the nucleus that give cells a prosurvival advantage. It is not necessarily specific to large cell lymphoma, but it targets the mechanism that large cell

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**APPROVAL SNAPSHOT**

**Tafasitamab-cxix**

**Accelerated approval: July 31, 2020**

Tafasitamab-cxix (Monjuvi) is indicated in combination with lenalidomide for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low-grade lymphoma, who are not eligible for autologous stem cell transplant.

**Efficacy data: L-MIND (NCT02399085)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tafasitamab plus lenalidomide (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response rate (95% CI)</td>
<td>55% (43%-67%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>37%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>18%</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>21.7 (0-24)</td>
</tr>
</tbody>
</table>

**Adverse events**

The most common adverse events (≥ 20%) are neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

*Efficacy population for approval was based on 71 patients treated in L-MIND.
*Most overall response rate was defined as the proportion of complete and partial responders as assessed by an independent review committee using the International Working Group (Cheson 2007) response criteria.
lymphoma probably uses to keep itself alive and potentially resistant,” Nathan H. Fowler, MD, said.

The drug’s approval was based on data from SADAL (NCT02227251), a multicenter, single-arm, open-label phase 2b trial in which 134 patients received selinexor 60 mg orally on days 1 and 3 of each week. All patients in the study had previously received 2 to 5 systemic regimens. Thirty-nine patients (29%) responded, with 18 (13%) achieving a CR and 21 (16%) achieving a PR. Unlike the L-MIND study, SADAL included patients with double- or triple-expressor status and data showed responses in these patients. “If you think about [selinexor in the context of] CAR T-cell data and others, it’s not quite as good, but it’s a single drug so it’s fairly easy to give. It is effective in a subset of patients with large cell lymphoma that is pretty difficult to treat, including patients who have double-hit lymphoma,” Fowler said. He also noted that responses appear durable. “If you look at patients who have PR or better, the duration of response is over 2 years, so there is a select group of patients who do achieve durable benefit with the drug,” he explained.

A challenge with selinexor is its toxicity. The most common grade 3 and 4 AEs observed in the SADAL study included thrombocytopenia (49% and 18%, respectively), neutropenia (21% and 9%), fatigue (grade 3/4, 16%), diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Grade 3/4 laboratory abnormalities (≥ 15%) are thrombocytopenia, lymphopenia, neutropenia, anemia, and hypotension.

The FDA recommends that selinexor be administered with antiemetic prophylaxis.7

The panelists emphasized that selinexor is not a replacement for CAR T-cell therapy but added that it may help fill an unmet need for patients who have limited treatment options. “For patients who are failing [ASCT or CAR T], we don’t have a lot of options. We can do lenalidomide and lenalidomide plus a CD19-targeted agent. Patients who fail CAR T-cell therapy, those who would not qualify [for CAR T], and those who are not near a [CAR T] center are the obvious population for selinexor,” Fowler said. Maddocks and Lunning agreed.

**EMERGING TREATMENTS AND TRENDS**

The panelists noted that many other agents are in clinical trials for R/R DLBCL, including bispecific antibodies such as glofitamab and epcoritamab. “[These are] going to be generating data but not a lot of data will follow [treatment with] CAR T,” Lunning said. Nevertheless, he is excited to see what kind of durability these drugs will ultimately show. In contrast, another investigational bispecific antibody, mosunetuzumab, has shown favorable efficacy in a phase 1/1b study that included patients with heavily pretreated R/R DLBCL, including those with disease progression after CAR T-cell therapy. Of the 7 evaluable patients with DLBCL who received prior CAR T-cell therapy, 2 achieved a CR.9

“When we were looking at the BITE [bispecific T-cell engager] molecule a couple of years ago, there was some sense that they would maybe displace CAR Ts. But a lot of the data that we’re seeing now are immature. I don’t think the durable CR rate appears to be at the same level that we’re seeing with CAR T, at least in large cell lymphoma. So, I don’t see these replacing CAR T-cell therapy, but I agree with Drs Maddocks and Lunning that they will probably follow CAR T as a salvage for these patients,” Fowler said.

The other treatment the panelists discussed were anti-CD19 antibody-drug conjugates (ADCs). “There are 3 CD19 ADCs that have been developed, all showing pretty similar responses; however, 2 are no longer being developed due to toxicity,” Maddocks said. She remarked that the third ADC had good initial responses but they were not durable. Subsequently, she noted this agent would probably have to be used as part of a combination therapy to achieve good remissions.

A major challenge in treating DLBCL is that there are no biological markers to guide treatment decision-making. “We really need to define the biology by some assay and then use that to put patients into different treatment groups. That’s the holy grail because a one-size-fits-all approach can only move the bar so much in large cell lymphoma,” Fowler said.

“It’s great that we’re getting all of these new drug classes—more drugs to have the discussions about,” Lunning said. “It’s a chess match against large cell lymphoma and it’s important to know what piece to play next. You may be moving 1 piece to make a move 3 turns down the road.”

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**APPROVAL SNAPSHOT**

**Selinexor**

**Accelerated approval: June 22, 2020**

**Selinexor (Xpovia)** is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

**Efficacy data: SADAL (NCT02227251)**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Selinexor (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (95% CI)</td>
<td>29% (22%-38%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>13%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>16%</td>
</tr>
<tr>
<td>Duration of response (n = 39)</td>
<td></td>
</tr>
<tr>
<td>Patients maintaining response at 3 months</td>
<td>56%</td>
</tr>
<tr>
<td>Patients maintaining response at 6 months</td>
<td>38%</td>
</tr>
<tr>
<td>Patients maintaining response at 12 months</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Adverse events**

The most common adverse events (≥ 20%) are fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Grade 3/4 laboratory abnormalities (≥ 15%) are thrombocytopenia, lymphopenia, neutropenia, anemia, and hypotension.

*As assessed by an independent review committee using Lugano 2014 criteria.

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**For a full list of references, see the article at OncLive.com.**
KRAS G12C occurs in 13% of patients (1 in 8) with NSCLC, comparable to the prevalence of all EGFR mutations.\(^1\)\(^2\) Identifying these patients and learning more about the KRAS G12C mutation is a high priority.

Learn more about Finding The UNSEEN 13 at FindKRASG12C.com

EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.


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