Myeloma Field Gears Up for a New Era

SAGAR LONIAL, MD

PEER EXCHANGE

GYNECOLOGIC CANCERS
4 Biomarker-Driven Regimens Hit Front Line

IMMUNOTHERAPY
TILs Move Closer to Market

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DANA-FARBER CANCER INSTITUTE
New Strategies Enhance Care in mUC
BY GURU P. SONPAVDE, MD
ZEJULA 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**

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

**Important Safety Information**

**Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)**, including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

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

**Hypertension and hypertensive crisis** have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, particularly coronary insufficiency, cardiac arrhythmias, and congestive heart failure, for the potential for serious adverse reactions from ZEJULA.

Closely monitor patients with cardiovascular disorders, periodically thereafter during treatment with ZEJULA. If hypertension occurs, adjust antihypertensive therapy as needed. Discontinue ZEJULA, and refer the patient to a cardiologist if hypertension is not adequately controlled with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Common lab abnormalities included increased AST (35%) and increased ALT (29%), decreased bilirubin (42%), constipation (40%), decreased magnesium (36%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased lymphocytes (51%), neutrophils (66%), decreased glucose (66%), increased cholesterol (71%), increased glucose (66%), muscular pain (39%), and leukopenia (28%).

**Embryo-Fetal Toxicity and Lactation**

Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential to avoid pregnancy and to use effective contraception during and for 1 month after receiving their final dose of ZEJULA. Advise males to use effective contraception during treatment with ZEJULA, and periodically thereafter. ZEJULA is excreted in breast milk; therefore, advise lactating women to not breastfeed during treatment with ZEJULA, and for 1 month after receiving the final dose of ZEJULA. Because breastfeeding can cause serious adverse reactions from ZEJULA in the infant, advise women to not breastfeed during treatment with ZEJULA, and for 1 month after receiving the final dose of ZEJULA.
PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS

OVERALL POPULATION

- **38%** REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH
  - MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR 0.62; 95% CI, 0.50-0.76) P<0.0001

HRD POPULATION

- **57%** REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH
  - MEDIAN PFS: 21.9 MONTHS WITH ZEJULA VS 10.4 MONTHS WITH PLACEBO (HR 0.43; 95% CI, 0.31-0.59) P<0.0001

**Study Design:** PRIMA, a randomized double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of once-daily ZEJULA versus placebo (2:1) in 733 women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to first-line platinum-based chemotherapy. The primary endpoint was a hierarchical calculation of PFS: first in patients with HRd tumors and then in all patients. PFS was measured from time of randomization to time of disease progression or death. At the time of PFS analysis, limited overall survival data were available with 11% deaths in the overall population.1,4

**Important Safety Information (continued)**

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

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

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

**References:**

1L, first-line; CI, confidence interval; CR, complete response; HR, hazard ratio; HRd, homologous recombination deficient; PFS, progression-free survival; PR, partial response.

Visit ZEJULA.COM/HCP to explore the PRIMA data

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NRPRNA200007 August 2020
Produced in USA.

Please see Brief Summary on the following pages.
BRIEF SUMMARY OF PRESCRIBING INFORMATION

ZELUZA (niraparib) capsules, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.ZELUZA.com.

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

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

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

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

1.3 Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

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

- a deleterious or suspected deleterious BRCA1 mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZELUZA monotherapy in clinical trials. In 1785 patients treated with ZELUZA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZELUZA in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.5 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiothereapy. Discontinue ZELUZA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

Hematologic adverse reactions (thrombocytopenia, anemia, and neutropenia) have been reported in patients treated with ZELUZA.

In PRIMA, the overall incidence of Grade 3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 35%, 31%, and 21% of patients receiving ZELUZA. 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 ZELUZA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZELUZA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. In NOVA, Grade >3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving ZELUZA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. In QUADRUM, Grade >3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving ZELUZA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 1% of patients.

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 1810 patients who received ZELUZA in the pooled PRIMA, NOVA and QUADRUM trials were nausea (65%), thrombocytopenia (65%), anemia (56%), fatigue (55%), constipation (19%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), diarrhea (14%), anorexia (13%), urinary tract infection (12%), and hyponatremia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

The safety of ZELUZA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZELUZA, the median duration of treatment was 11.1 months (range: 0.1 to 29 months).

All Patients Receiving ZELUZA in PRIMA

Serious adverse reactions occurred in 12% of patients receiving ZELUZA. Serious adverse reactions in >2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.5%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and plural effusion (see patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZELUZA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZELUZA included thrombocytopenia (5.7%), anemia (1.9%), nausea and neutropenia (1.2% each). Adverse reactions led to dose reduction or interruption in 40% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

Table 1 and 2 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in all patients treated with ZELUZA in the PRIMA study.

| Table 1. Adverse Drug Reactions Reported in ≥1% of All Patients Receiving ZELUZA in PRIMA* |
|----------------------------------|----------|----------|----------|----------|----------|----------|
|                                 | Grades 1-4 | Grades 3-4 |
|                                  | ZELUZA    | Placebo  | ZELUZA   | Placebo  |
| Blood and Lymphatic System Disorders |          |          |          |          |
| Thrombocytopenia                  | 66/5      | 9/1      | 39/3     | 0.4/1    |
| Anemia                            | 64/10     | 8/3      | 18/2     | 1/0      |
| Neutropenia*                      | 47/2     | 8/2      | 21/3     | 1/0      |
| Leukopenia*                       | 28/9      | 5/0      | 4/1      | 0.4/1    |
| Gastrointestinal Disorders        |          |          |          |          |
| Nausea                            | 57/1      | 2/1      | 1/1      | 0.4/1    |
| Constipation                      | 40/2      | 20/1     | 1/0      | 0.4/1    |
| Vomiting                          | 22/2      | 12/1     | 1/1      | 0.4/1    |
| General Disorders and Administration Site Conditions |          |          |          |          |
| Fatigue                           | 51/1      | 41/1     | 3/1      | 1/0      |
| Investigations                    | 14/1      | 7/1      | 3/0      | 0.4/1    |
| Metabolism and Nutrition Disorders |          |          |          |          |
| Decreased appetite                | 10/1      | 8/1      | 1/0      | 0.4/1    |
| Musculoskeletal and Connective Tissue Disorders |          |          |          |          |
| Musculoskeletal pain              | 39/1      | 38/1     | 1/0      | 0.4/1    |
| Nervous System Disorders          |          |          |          |          |
| Headache                          | 26/4      | 15/4     | 0.4/0    | 1/0      |
| Dizziness                         | 19/3      | 18/3     | 0.4/0    | 1/0      |
| Psychiatric Disorders             |          |          |          |          |
| Insomnia                          | 25/1      | 15/1     | 0.4/0    | 1/0      |
| Renal and Urinary Disorders       |          |          |          |          |
| Acute kidney injury*              | 12/5      | 5/2      | 0.4/0    | 1/0      |
| Respiratory, Thoracic and Mediastinal Disorders |          |          |          |          |
| Dyspnea                           | 22/13     | 13/1     | 0.4/0    | 1/0      |
| Cough                             | 18/15     | 10/0     | 0.4/0    | 1/0      |
| Vascular Disorders                |          |          |          |          |
| Hypertension                      | 18/7      | 7/6      | 6/1      | 1/0      |

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

CIEA=Common Terminology Criteria for Adverse Events version 4.02.

Includes neutropenia, neutropenic infection, neutropenia sipsis, 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 creatine increased. 
### Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELURA in PRIMA

<table>
<thead>
<tr>
<th>Grade</th>
<th>ZELURA (N=367)</th>
<th>Placebo (N=179)</th>
<th>Placebo (N=179)</th>
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<tbody>
<tr>
<td>Grades 1-4</td>
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<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
<td>66</td>
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<tr>
<td>Decreased platelets</td>
<td>74</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71</td>
<td>36</td>
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<tr>
<td>Increased glucose</td>
<td>65</td>
<td>57</td>
<td>3</td>
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<tr>
<td>Decreased neutrophils</td>
<td>66</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51</td>
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<td>Increased alkaline phosphatase</td>
<td>46</td>
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<td>Decreased creatinine</td>
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<td>Increased aspartate aminotransferase</td>
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<td>1</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>29</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

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

Among patients who received ZELURA with the dose based on weight and platelet count, the median duration of treatment was 11.0 months (range: 1 day to 16 months).

Serious adverse reactions occurred in 27% of patients receiving ZELURA. Serious adverse reactions were observed in ≥2% of patients and included anemia (8%), thrombocytopenia (7%), and febrile neutropenia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZELURA. Adverse reactions resulting in permanent discontinuation occurred in <2% of patients who received ZELURA. These included thrombocytopenia and anemia (3.0% each) and nausea (2.4%).

Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Tables 3 and 4 summarize adverse reactions and abnormal laboratory findings in the group of patients who received ZELURA.

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

<table>
<thead>
<tr>
<th>Grade</th>
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<th>Placebo (N=179)</th>
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<tbody>
<tr>
<td>Grades 1-4</td>
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<tr>
<td>Decreased hemoglobin</td>
<td>81</td>
<td>70</td>
<td>21</td>
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<td>Decreased platelets</td>
<td>79</td>
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<td>Increased glucose</td>
<td>63</td>
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<td>18</td>
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<td>Decreased creatinine</td>
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<td>43</td>
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<tr>
<td>Increased alanine aminotransferase</td>
<td>31</td>
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### Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELURA Based on Baseline Weight or Platelet Count in PRIMA

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<thead>
<tr>
<th>Grade</th>
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<th>Placebo (N=179)</th>
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<tbody>
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<td>Decreased hemoglobin</td>
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<tr>
<td>Decreased platelets</td>
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<td>Increased glucose</td>
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<tr>
<td>Increased creatinine</td>
<td>28</td>
<td>11</td>
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### Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZELURA in NOVA

<table>
<thead>
<tr>
<th>Grade</th>
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<th>Placebo (N=179)</th>
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<td>Increased AST</td>
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<tr>
<td>Increased ALT</td>
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### Table 6: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELURA in NOVA

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<th>Grade</th>
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<td>Increased neutrophils</td>
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<td>20</td>
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</table>

**Cardiac Disorders**
- Palpitations
- Arrhythmias
- Chest pain

**Gastrointestinal Disorders**
- Nausea
- Vomiting
- Diarrhea

**Respiratory, Thoracic and Mediastinal Disorders**
- Dyspnea

**Nervous System Disorders**
- Headache
- Dizziness

**Metabolism and Nutrition Disorders**
- Decreased appetite

**Hypertension**

**Other Reactions**
- Baseline elevations
- Rash

**Treatment of Recurrent Ovarian Cancer**

The safety of ZELURA 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 ZELURA in these patients was 250 days.
Tuberculosis includes events with preferred terms of tuberculosis and pleural cavity decreased.

Table 6: Abnormal Laboratory Findings in ≥ 25% of Patients Receiving ZELENA in QUADRA

<table>
<thead>
<tr>
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<td>Decreased albumin</td>
<td>27</td>
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6.2 Postmarketing Experience

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


8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZELENA 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 ZELENA in pregnant women. Inform the patient or caregiver of the potential risk to the fetus.

Instruct patients to use effective contraception during treatment with ZELENA. Data from preclinical animal studies show that ZELENA can cause fetal harm when administered during the first trimester of pregnancy [see Animal Data (14.1)]. ZELENA should only be administered to pregnant women if the potential benefit justifies the potential risk to the fetus.

8.2 Lactation

Risk Summary

There are no data regarding the potential for ZELENA to be present in breast milk. The decision to breastfeed should be based on a careful balance of the potential benefits of breastfeeding versus the potential risks of ZELENA to the nursing infant.

8.3 Children

The safety and efficacy of ZELENA have not been established in children.

8.4 Safe Use in Elderly

In clinical trials, ZELENA was generally well tolerated by elderly patients. No dosage adjustment is required based on age.

8.5 Geriatric Use

Of 1589 patients aged ≥ 65 years, 11% were aged ≥ 75 years. No overall differences in safety and effectiveness were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage adjustment is necessary for patients with mild (Clcr 60 to 89 mL/min) or 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 ZELENA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria. The safety of ZELENA in patients with severe hepatic impairment is not determined.

10 OVERDOSAGE

There is no specific treatment for overdose with ZELENA. Overdose symptoms may include nausea, vomiting, dizziness, drowsiness, and diarrhea. Provide general supportive measures and monitor the patient for signs and symptoms of overdose. If an overdose is suspected, immediately consult poison control centers for specific guidance.

11 PATIENT COUNSELING INFORMATION

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

Medication Instructions

Advise patients to take the medication as directed. Do not take more than the recommended dose. Store in a cool, dry place and out of reach of children.

Use as directed. Do not exceed the prescribed dose. Do not use for longer than recommended. Do not share with others.

Inform patients about the potential adverse effects of ZELENA. If any of these symptoms occur, advise patients to seek medical attention immediately.

Confidentiality

Inform patients that their health information is confidential and may be shared with healthcare providers for the purpose of monitoring adherence and for research purposes.

12 Dosing Instructions

Inform patients on how to take ZELENA (see Dosage and Administration (2.2) of full prescribing information). ZELENA should be taken once daily. Instruct patients to take the medication with food. Advise patients to take ZELENA at the same time each day.

13 Contraindications

ZELENA is contraindicated in patients with a history of hypersensitivity to ZELENA or its components. ZELENA should not be administered to patients with renal failure (Clcr < 30 mL/min) or hepatic failure.

14 Precautions

Inform patients that they should not take ZELENA with certain medications, such as those that may increase liver damage.

15 Adverse Reactions

Adverse reactions are listed in the following tables. The frequency of adverse reactions is based on the percentage of patients experiencing the reaction.

Table 1: Common Terminology Criteria for Adverse Events version 4.02

<table>
<thead>
<tr>
<th>Grade</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anemia</td>
<td>Decreased</td>
</tr>
<tr>
<td>2</td>
<td>Diarrhea</td>
<td>Increased</td>
</tr>
<tr>
<td>3</td>
<td>Insomnia</td>
<td>Increased</td>
</tr>
<tr>
<td>4</td>
<td>Acute Kidney Injury</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Table 2: Grade 3 and 4 Adverse Reactions Reported in ≥ 5% of Patients Receiving ZELENA

<table>
<thead>
<tr>
<th>Grade 3-4</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=663</td>
<td>Anemia</td>
<td>Increased</td>
</tr>
<tr>
<td>N=663</td>
<td>Diarrhea</td>
<td>Increased</td>
</tr>
<tr>
<td>N=663</td>
<td>Insomnia</td>
<td>Increased</td>
</tr>
<tr>
<td>N=663</td>
<td>Acute Kidney Injury</td>
<td>Increased</td>
</tr>
</tbody>
</table>

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

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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 46.
Myeloma Field Gears Up for a New Era

by ANITA T. SHAFFER

Sagar Lonial, MD, a 2020 Giants of Cancer Care® award winner whose research has helped improve outcomes for patients with multiple myeloma, discusses the potential for emerging therapies that target B-cell maturation antigen and trends likely to influence care across cancer types. He serves as a cochair for the 25th Annual International Congress on Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Myeloma in February 2021.
New Myeloma Milestones Are in the Works

DURING THE PAST 2 DECADES, the introduction of novel therapies and improvements in treatment strategies has enhanced outcomes markedly for patients with multiple myeloma (MM). The impact of these advancements was captured in a study that compared outcomes among people treated for MM at Mayo Clinic in Rochester, Minnesota, between 2004 and 2017. The estimated 4-year survival rate increased from 50% among patients who received diagnoses from 2004 through 2007 to 75% among those treated from 2013 to 2017.1

For a simpler yet evocative measure of the pace of the changes that have helped bring about results like these, consider this: During a 2-week period in November 2015, the first-ever monoclonal antibodies for the treatment of MM, daratumumab (Darzalex) and elotuzumab (Empliciti), gained FDA approval, along with a new oral proteasome inhibitor, ixazomib (Ninlaro).2 Since then, many studies have produced findings that refine the use of these agents, transforming the treatment paradigm for MM.

Now we appear to be poised to take another significant step forward in MM therapy. In August, the FDA approved belantamab mafodotin-blmf (Blenrep), the first therapy to target B-cell maturation antigen (BCMA).3 Several other BCMA-directed approaches are in the late stages of clinical development, so we are likely just at the beginning of a new class of therapeutics.

Our cover story in this issue of OncologyLive®, Sagar Lonial, MD, describes the implications that BCMA-targeted therapies could have in MM. He is uniquely qualified to talk about these developments: His research helped pave the way for the approvals of daratumumab, elotuzumab, and belantamab mafodotin, and he was recognized this year with a Giants of Cancer Care® award in the myeloma category.

Lonial’s comments help set the stage for the 62nd American Society of Hematology Annual Meeting and Exposition from December 5 to 8, and for the 25th Annual International Congress on Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Myeloma from February 25 to February 28, 2021. Both meetings will take place in virtual formats. Please check out OncLive.com for all the breaking news from these meetings and other research developments.

As always, thank you for reading.
Mike Hennessy Sr
Chairman and Founder

REFERENCES
Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6% in adult patients with MDS with normal baseline blood pressure. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Hypertension
Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6%. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity
REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

ADVERSE REACTIONS
Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients.

The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection.

LACTATION
It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

Please see the Brief Summary of full Prescribing Information for REBLOZYL on the following pages.

1 INDICATIONS AND USAGE

1.2 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

REBLOZYL (luspatercept-aamt) is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 3 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

1.3 Limitations Of Use

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage for Myelodysplastic Syndromes with Ring Sideroblasts (MDS-RS) or Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T) Associated Anemia

The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by subcutaneous injection for patients with anemia of MDS-RS or MDS/MPN-RS-T. Prior to each REBLOZYL dose, review the patient’s hemoglobin and transfusion record. Titrate the dose based on responses according to Table 3. Interrupt treatment for adverse reactions as described in Table 4. Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

If a planned administration of REBLOZYL is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

Dose Modifications for Response

Assess and review hemoglobin results prior to each administration of REBLOZYL. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation.

If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the REBLOZYL dose to 1.33 mg/kg (Table 3). If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose level, increase the REBLOZYL dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

If the increase in hemoglobin is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.

Dose modifications for response are provided in Table 3.

Table 3: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dose Titration for Response

<table>
<thead>
<tr>
<th>REBLOZYL</th>
<th>Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>* 1 mg/kg every 3 weeks</td>
</tr>
<tr>
<td>Dose Increases for Insufficient Response at Initiation of Treatment</td>
<td></td>
</tr>
<tr>
<td>Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose</td>
<td>* Increase the dose to 1.33 mg/kg every 3 weeks</td>
</tr>
<tr>
<td>Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg starting dose</td>
<td>* Increase the dose to 1.75 mg/kg every 3 weeks</td>
</tr>
<tr>
<td>No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg</td>
<td>* Discontinue treatment</td>
</tr>
</tbody>
</table>

Dose Modifications for Predose Hemoglobin Levels or Rapid Hemoglobin Rise

Predose hemoglobin is greater than or equal to 11.5 g/dL in the absence of transfusions

* Interrupt treatment
* Restart when the hemoglobin is no more than 11 g/dL.

Increase in hemoglobin greater than 2 g/dL within 3 weeks in the absence of transfusions and

* current dose is 1.75 mg/kg
* current dose is 1.33 mg/kg
* current dose is 1 mg/kg
* current dose is 0.8 mg/kg
* current dose is 0.6 mg/kg

* Reduce dose to 1.33 mg/kg
* Reduce dose to 1.0 mg/kg
* Reduce dose to 0.8 mg/kg
* Reduce dose to 0.6 mg/kg
* Discontinue treatment

* Do not increase the dose if the patient is experiencing an adverse reaction as described in Table 4.

Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 4.

Table 4: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dosing Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>REBLOZYL</th>
<th>Dosing Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 hypersensitivity reactions</td>
<td>* Discontinue treatment</td>
</tr>
</tbody>
</table>
| Other Grade 3 or 4 adverse reactions | * Interrupt treatment
* When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level**
* If the dose delay is >12 consecutive weeks, discontinue treatment

**Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

**For Table 3 dose reductions above.

4 CONTRAINDICATIONS

None.
Luspatercept-aamt was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are no data on the presence of REBLOZYL (luspatercept-aamt) in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with REBLOZYL, and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

REBLOZYL may cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with REBLOZYL and for at least 3 months after the last dose.

Infertility

Females

Based on findings in animals, REBLOZYL may impair female fertility [see Nonclinical Toxicology (13.1)]. Adverse effects on fertility in female rats were reversible after a 14-week recovery period.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Based on findings in juvenile animals, REBLOZYL is not recommended for use in pediatric patients [see Non-Clinical Toxicology (13.1)].

8.5 Geriatric Use

Clinical studies of REBLOZYL in beta thalassemia did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

Clinical studies of REBLOZYL for treatment of anemia in MDS-RA and MDS/MPN-RAS-T included 206 (79%) patients ≥65 years of age and 93 (36%) patients ≥75 years of age. No differences in safety or effectiveness were observed between older (>65 years) and younger patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with luspatercept-aamt. In a repeat-dose toxicity study, juvenile rats were administered luspatercept-aamt subcutaneously at 1, 3, or 10 mg/kg once every 2 weeks from postnatal day 7 to 91. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at 10 mg/kg resulting in exposures (based on area under the curve [AUC]) approximately 4.4 times the maximum recommended human dose (MRHD) of 1.75 mg/kg. 

In a combined male and female fertility and early embryonic development study in rats, luspatercept-aamt was administered subcutaneously to animals at doses of 1 to 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-aamt-treated females.

Effects on female fertility were observed at the highest dose with exposures (based on AUC) approximately 7-times the MRHD of 1.75 mg/kg. Adverse effects on fertility in female rats were reversible after a 14-week recovery period. No adverse effects were noted in male rats.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with REBLOZYL.

Thromboembolic Events

Advise beta-thalassemia patients of the potential risk of thromboembolic events. Review known risk factors for developing thromboembolic events and advise patients to reduce modifiable risk factors (e.g., smoking, use of oral contraceptives) [see Warnings and Precautions (5.1)].

Effects on Blood Pressure

Caution patients that REBLOZYL may cause an increase in blood pressure [see Warnings and Precautions (5.2)].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving REBLOZYL and for at least 3 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with REBLOZYL [see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)].

Lactation

Advise females not to breastfeed during treatment with REBLOZYL and for 3 months after the final dose [see Use in Specific Populations (8.2)].
Real-World Impact of Low-Grade AEs Needs a Closer Look

by MAURIE MARKMAN, MD

ONE OF THE MOST EXCITING developments in anticancer therapeutics over the past decade has been the development of a novel class of drugs designed to interfere with PARP, a critical DNA repair mechanism. Preclinical studies and multiple clinical trials have revealed the rather exquisite sensitivity of malignant cells with inherent deficiencies in another DNA repair mechanism, homologous recombination.

The primary clinical setting in which this drug class has shown relevance is in individuals with documented germline or somatic mutations in BRCA1 or BRCA2 genes. This includes a quite meaningful percentage of patients with cancers of the ovary and breast. More recently, PARP inhibitors have demonstrated a favorable impact in men with prostate cancer and a BRCA mutation, as well as in both men and women with pancreas cancer who also possess this genetic abnormality. It is important to note that PARP-inhibiting agents are also clinically active in settings where other types of inherent DNA repair deficiencies are present.

The magnitude of the clinical benefit associated with the delivery of these oral agents as a potentially long-term maintenance strategy is emphasized in the results of a number of phase 3 randomized studies that examined PARP inhibitor therapy following a response to primary or second-line platinum-based chemotherapy in advanced ovarian cancer. In women with documented BRCA mutations, the progression-free survival hazard ratios for active treatment, compared with placebo, have been in the 0.30 or even lower range (a 70% improvement), an impressive clinical outcome for any antineoplastic agent in an advanced or metastatic human malignancy.

Further, the potential clinical benefits associated with an oral agent are clear, especially considering the effectiveness of these drugs, which may be taken continuously by an individual patient for several or possibly even many years. The benefit to a patient and their family associated with the ability to take “pills” at home, one or several times a day, versus being required to travel to a clinic, physician’s office, infusion center, or hospital every few weeks for intravenous therapy, possibly spending many hours in the process for each individual treatment, are surely obvious.

However, we should consider the adverse effect (AE) profile of oral PARP inhibitors. Although these agents are generally reasonably well tolerated, certainly compared with platinum and other routinely employed cytotoxic antineoplastic drugs, the majority of patients receiving PARP inhibitors in multiple reported clinical trials reported low-grade (1 or 2) nausea and fatigue. These studies routinely report a high proportion of individuals requiring dose modifications during the course of treatment; however, the percentage of individuals discontinuing PARP inhibitors in various studies, regardless of the specific agent employed, is quite modest (in the range of 10%). Further, studies conducted during the various trials have consistently suggested no meaningful decrement in overall quality of life for patients taking active treatment versus placebo.

INSIGHTS FROM ADHERENCE FAILURES

So is there a problem here? The issue is not what could be accomplished within the confines of a clinical trial, where patients are carefully and routinely monitored and counseled, but rather what actually happens in the real world to individuals who are asked to take “pills” once or...
several times every day, and who regularly experience such low-grade symptoms as nausea and fatigue. In the maintenance setting, it must be remembered that these individuals are not experiencing any symptoms of cancer (which this class of medication may have caused to disappear) and they may be asked to take the drug for years, possibly experiencing the low-grade AEs during this entire period.

Unfortunately, a review of the literature regarding adherence to the long-term administration of oral antineoplastic agents for which low-grade but persistent AEs are observed is not reassuring. For example, a recent report examining adherence to oral adjuvant aromatase inhibitors among more than 700 patients with breast cancer found that at 3 years, only 55.5% met the prospectively defined definition of adherence.4 The study, which revealed almost half of this large population was nonadherent, is particularly meaningful because this end point was based on the measurement of urine aromatase metabolites, rather than simply asking patients if they were reliably taking the prescribed medications. These results are surely disturbing and contain a message for patients treated with PARP inhibitors, since it is quite possible survival outcomes among the nonadherent population would be affected negatively.

In fact, in a separate study that examined more than 1100 patients receiving adjuvant tamoxifen and monitored adherence by tamoxifen serum levels, 16% were nonadherent, with evidence that failure to take the prescribed medication had a significant negative impact on survival outcomes.5 Finally, experience with imatinib (Gleevec), the paradigm-changing oral therapy for patients with chronic myeloid leukemia, has similarly revealed that adherence to treatment has a substantial influence on the ability of a patient to remain in clinical remission.6

The oncology community needs to carefully consider the implications of these low-grade AEs observed during the long-term delivery of oral antineoplastic therapy. In fact, in the context of prolonged administration when patients may routinely experience such effects, the use of the term low grade to describe the phenomena is probably highly misleading. This issue with PARP inhibitors needs further investigation to both document what happens in the real world and, most importantly, to discover effective strategies to improve adherence to optimize the documented benefits of this class of anticancer drugs.

REFERENCES
FoundationOne Liquid CDx Gains 3 New Indications

The FDA has approved the FoundationOne Liquid CDx for use as a companion diagnostic for 3 targeted therapies: alpelisib (Picray) in advanced or metastatic breast cancer, rucaparib (Rubraca) in advanced ovarian cancer, and alectinib (Alecensa) in patients with metastatic non–small cell lung cancer harboring an ALK mutation.

The agency also gave the green light to a label expansion for the diagnostic to report additional select copy number alterations and genomic rearrangements. The companion diagnostic evaluates guideline-recommended genes and is capable of evaluating more than 300 genes. It uses a blood-based biopsy that reports blood tumor mutational burden, microsatellite instability, and tumor fraction values.

In August 2020, FoundationOne Liquid CDx was approved by the FDA for all solid tumors with multiple companion diagnostic indications. The decision was based on data from analytical and clinical validation studies that collected more than 7500 samples and 30,000 unique variants spanning more than 30 tumor types. The test was shown to have high sensitivity and specificity, even at the low allele frequencies observed in the blood samples that were collected for analysis.


Larotrectinib Tacks on Companion Diagnostic to Identify NTRK+ Tumors

The FDA has approved the FoundationOne CDx comprehensive genomic test as a companion diagnostic for larotrectinib (Vitrakvi) to identify patients with NTRK1/2/3 gene fusions across all solid tumors.

FoundationOne CDx is the sole FDA-approved tissue-based comprehensive genomic profiling assay that is indicated to detect NTRK1/2/3 fusions across all solid malignancies, and identify those individuals who may be appropriate for treatment with the TRK inhibitor.

Larotrectinib is approved for adult and pediatric patients with solid tumors who have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or who have progressed following therapy.


Trastuzumab Deruxtecan Is Granted Priority Review in HER2+ Gastric Cancer

The FDA has granted a priority review designation to a supplemental biologics license application for the antibody-drug conjugate (ADC) fam-trastuzumab deruxtecan-nxki (Enhertu) for patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma. The agency is expected to make a decision in the first quarter of 2021.

The application was based on data from the phase 2 DESTINY-Gastric01 trial (NCT03329690), which showed that the ADC elicited an objective response rate of 51.3% compared with 14.3% with chemotherapy in patients in this population who had progressed following trastuzumab (Herceptin)-containing treatment.

The ADC also led to a longer median overall survival compared with chemotherapy, at 12.5 months versus 8.4 months, respectively. Additionally, median PFS and median duration of confirmed response proved to be longer with trastuzumab deruxtecan.


Nivolumab/Cabozantinib Combo Lands Priority Status in Advanced RCC

The FDA has granted a priority review designation to a supplemental biologics license application and supplemental new drug application for nivolumab (Opdivo) plus cabozantinib (Cabometyx) for the treatment of patients with advanced renal cell carcinoma (RCC), according to developers Bristol Myers Squibb and Exelixis, Inc.

The applications are based on data from the phase 3 CheckMate 9ER trial (NCT03141177), which showed that the combination resulted in a 49% reduction in the risk of disease progression or death, significantly improving overall survival versus sunitinib (Sutent) when used as a frontline treatment in patients with RCC (16.6 vs 8.3 months, respectively; HR, 0.51; P < .0001). Nivolumab/cabozantinib doubled objective response rates in this setting (55.7% vs 27.1%, respectively; P < .0001). Further, in the investigational arm, the complete response rate was 8.0%, the partial response rate was 47.7%, and the stable disease rate was 32.2%.

The combination also demonstrated a tolerable toxicity profile, with a low rate of drug-related discontinuations in patients with advanced disease. The FDA is expected to make a decision on the applications by February 20, 2021.

TO READ MORE, VISIT https://bit.ly/3keifQg.

Cemiplimab Undergoes Review for Advanced NSCLC With High PD-L1 Expression

The FDA has granted a priority review designation to a supplemental biologics license application for cemiplimab-rwlc (Libtayo) for the frontline treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with a PD-L1 expression level of 50% or greater.

The application is based on data from EMPOWER-Lung1 (NCT03088540), a phase 3 trial testing single-agent cemiplimab with platinum-doublet chemotherapy in this patient population. Results showed that cemiplimab resulted in a 43% reduction in the risk of death in the subset of patients with high PD-L1 expression (HR, 0.57; 95% CI, 0.42-0.77; P < .0002). In the overall trial population, the PD-1 inhibitor reduced the risk of death by 32% (HR, 0.68; 95% CI, 0.53-0.87; P < .0022).

The FDA is expected to make a decision by February 28, 2021.

TO READ MORE, VISIT https://bit.ly/389aAPV.

Osimertinib Moves Toward Approval for Early-Stage EGFR+ Lung Cancer

Osimertinib (Tagrisso) will be evaluated under a priority review designation for a supplemental new drug application for the adjuvant treatment of patients with early-stage EGFR-mutated non–small cell lung cancer (NSCLC) following complete tumor resection with curative intent. The FDA is scheduled to make a decision during the first quarter of 2021.

The application is based on findings from the phase 3 ADAURA trial (NCT02511106), which showed that adjuvant osimertinib resulted in a statistically significant and clinically meaningful improvement in disease-free survival in patients with stage IB/II/IIIA EGFR-mutated NSCLC. Use of the targeted agent resulted in a 79% reduction in the risk of disease recurrence or death (HR, 0.21; 95% CI, 0.16-0.28; P < .0001) in the overall population. Data for overall survival are still immature and the median has not yet been reached in either arm of the study.

TO READ MORE, VISIT https://bit.ly/3ef5v3F.
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**TUNE IN!**

In our exclusive interview, Dr. Dizon discusses the primary physical and residual psychological effects of gynecologic cancers on women’s sexual health, the challenges of broaching these topics in the clinic, and the role oncologists play in helping patients manage these difficulties.
**Drug Spotlight | CAPMATINIB (TABRECTA)**

**MET**

**ex14+ NSCLC Armamentarium Welcomes First Targeted Therapy**  
by RACHEL NAROZNIAK, MA

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**The First Biomarker-Driven Intervention** for patients with non–small cell lung cancer (NSCLC) whose tumors harbor a **MET** exon 14 (**MET**ex14) skipping mutation is now available in clinical practice.

On May 6, 2020, the FDA granted an accelerated approval to capmatinib (Tabrecta) for adults who have metastatic NSCLC with a mutation that leads to **MET**ex14, as detected by an FDA-approved test. The agency concurrently approved Foundation Medicine’s FoundationOne CDx assay as a companion diagnostic for capmatinib.1

The approval of capmatinib for patients with **MET**ex14-mutant advanced NSCLC is based on overall response rate (ORR) and response duration data from the phase 2 GEOMETRY mono-1 trial (NCT02414139). The safety and efficacy of capmatinib were evaluated in a subpopulation of 97 patients, who received 400 mg of capmatinib twice daily.

Among the trial’s 28 treatment-naïve patients, the ORR was 68% (95% CI, 48%-84%), with a response duration of 12.6 months (95% CI, 5.5-25.3).1 In the 69 patients who received prior treatment, the ORR was 41% (95% CI, 29%-53%). The response duration in this subgroup was 9.7 months (95% CI, 5.5-13.0).2 Continued approval may be contingent on verification and clinical benefit observed in confirmatory trials.

Capmatinib is the first therapy specifically approved to target **MET**ex14 mutations in NSCLC, which have been observed in 3% to 4% of cases.3 The agent also was evaluated in patients with **MET** amplifications, which occur in 1% to 6% of NSCLCs, as part of GEOMETRY mono-1.4

In patients with **MET** amplifications with a gene copy number of 10 or higher, the ORR was 29% (95% CI, 19%-41%) for those previously treated and 40% (95% CI, 16%-18%) for those without prior therapy. Efficacy was limited at lower expression levels.5

In an interview with OncologyLive®, Edward B. Garon, MD, an author on the GEOMETRY mono-1 trial and an associate professor of medicine in the Division of Hematology/Oncology at the David Geffen School of Medicine at the University of California, Los Angeles, discussed the therapy’s tolerability and its groundbreaking contribution to the NSCLC tool kit.

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**Why is the approval of capmatinib meaningful for this molecularly specific patient subgroup?**

Capmatinib is approved specifically for patients with **MET** exon 14 deletions [which can cause **MET**ex14 mutations]. For decades, **MET** has been recognized as an oncogene with the potential to drive tumors.

Generally, patients with these deletions do not have particularly good prognoses, and this is also a population of patients that does not [respond well] to standard chemotherapy. Similarly, it is a group that does not tend to have great responses to immunotherapy [based on] available data.

This is not a particularly rare group of tumors. The patient population tends to be a little older than what is seen in other oncogene-driven tumors and is more similar to what we see in the general lung cancer population.

---

**Please discuss the efficacy data that led to the approval.**

The efficacy data for the approval was based on 2 cohorts of the GEOMETRY mono-1 study. One cohort [included] patients who received prior therapy; the other cohort, patients who were treatment naïve. In the prior chemotherapy group, the response rate was over 40%. The response rate was about two-thirds in patients who were treatment naïve. Both of these response rates would be better than what would be [possible] with standard therapy.

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**How well are patients able to tolerate capmatinib?**

In general, capmatinib’s toxicity profile was quite good in the GEOMETRY mono-1 study. Patients were able to tolerate the drug well, and most did not require dose reduction. The dosing for capmatinib is 400 mg twice daily.

The most common toxicity with capmatinib is peripheral edema, and although in some cases it could be quite significant, in most cases it was grade 1 or grade 2. Overall, other toxicities have been less common.

---

**How does this approval advance the paradigm?**

This is the first agent that is approved for this population of patients, [and notably, it] is the first biomarker-directed therapy for these patients. This group would be eligible for other standard therapies, so prior to this approval, patients would probably be receiving combinations of chemotherapy, although the role of immunotherapy in this population is not entirely well known.

That would be the frontline [therapy]; second-line approaches would include docetaxel-based chemotherapies. For patients with **MET**ex14 skipping–mutant NSCLC, capmatinib would be a very appropriate [agent] to consider as part of initial therapy, as well as for patients who previously received other therapies and are now progressing on those therapies.

---

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

We still do not have much available data. The GEOMETRY mono-1 was a very large study that also looked at the role of capmatinib in patients who had amplification of the **MET** gene. I think evaluating the [agent] in that group of patients will be important. Combinations of capmatinib and other drugs that could enhance both the response rate and duration of response [will likely also be explored].

---

**References**

1. FDA approves first targeted therapy to treat aggressive form of lung cancer. FDA. May 6, 2020.  


   doi:10.1056/NEJMoa2002787

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**Drug Spotlight | CAPMATINIB (TABRECTA)**

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**MET**

ex14+ NSCLC Armamentarium Welcomes First Targeted Therapy

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**References**

1. FDA approves first targeted therapy to treat aggressive form of lung cancer. FDA. May 6, 2020.  


   doi:10.1056/NEJMoa2002787
PIVOTAL CLINICAL TRIAL

GEOMETRY mono-1 (NCT02414139), a nonrandomized, multicohort study, enrolled 97 patients with MET exon 14-mutant, EGFR wild-type, and ALK-negative NSCLC with at least 1 measurable lesion by RECIST 1.1 criteria. Patients with symptomatic central nervous system metastases, clinically significant uncontrolled cardiac disease, or who received prior therapy with a MET inhibitor or HGF inhibitor were excluded.

BASELINE PATIENT CHARACTERISTICS

Median age, (years, range)

<table>
<thead>
<tr>
<th>Cohort 4, previously treated (n = 69)</th>
<th>Cohort 5b, treatment naïve (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71 (49-90)</td>
<td>71 (57-86)</td>
</tr>
</tbody>
</table>

Prior lines of antineoplastic therapy (%)

<table>
<thead>
<tr>
<th>Cohort 4 (n = 69)</th>
<th>Cohort 5b (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: 73.9%</td>
<td>89%</td>
</tr>
<tr>
<td>2: 23.2%</td>
<td>7%</td>
</tr>
<tr>
<td>3: 2.9%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Histology (%)

<table>
<thead>
<tr>
<th>Cohort 4 (n = 69)</th>
<th>Cohort 5b (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77%</td>
<td>89%</td>
</tr>
<tr>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>9%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Metastatic site of cancer (%)

<table>
<thead>
<tr>
<th>Brain*</th>
<th>Adrenal</th>
<th>Liver</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.9%</td>
<td>15.9%</td>
<td>23.2%</td>
<td>59.4%</td>
</tr>
</tbody>
</table>

DOR, duration of response; ORR, overall response rate.

Efficacy results in the GEOMETRY MONO-1 trial

Outcome | Treatment-naive patients (cohort 5b; n = 28) | Previously treated patients (cohort 4; n = 69)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>68% (48%-84%)</td>
<td>41% (29%-53%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Partial response</td>
<td>64%</td>
<td>4%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>12.6 (5.5-25.3)</td>
<td>9.7 (5.5-13.0)</td>
</tr>
<tr>
<td>DOR ≥ 12 months</td>
<td>47%</td>
<td>32%</td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

- Interstitial lung disease/pneumonitis
- Risk of photosensitivity
- Hepatotoxicity
- Embryo-fetal toxicity
- Dyspnea

COMMONLY REPORTED ADVERSE EVENTS IN GEOMETRY MONO-1 TRIAL

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Capmatinib (N = 334, all cohorts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>52%</td>
</tr>
<tr>
<td>Nausea</td>
<td>44%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28%</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>24%</td>
</tr>
<tr>
<td>Constipation</td>
<td>18%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
</tr>
<tr>
<td>Cough</td>
<td>16%</td>
</tr>
<tr>
<td>Back pain</td>
<td>14%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14%</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Grade 4 dyspnea was reported in 0.6% of patients.
For adults with intermediate- or high-risk myelofibrosis (MF)

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 10^9/L.‡

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

†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 MIPI-70 (threshold of ≤3 prognostic variable points), and very low, low, or intermediate risk based on MIPI-70+ (version 2.0; threshold of ≤3 prognostic variable points).§

‡In patients who are not transplant candidates.

**SIGNIFICANTLY MORE PATIENTS RECEIVING JAKAFI EXPERIENCED IMPROVEMENT IN MF-RELATED SPLENOMEGALY**

**COMFORT-I PRIMARY ENDPOINT**

42% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24 VS 0.7% of patients receiving placebo (P < 0.0001)

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

**COMFORT-II PRIMARY ENDPOINT**

29% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 48 VS 0% of patients receiving best available therapy (P < 0.0001)

48% of patients randomized to best available therapy were eligible to cross over to receive Jakafi because of disease progression or unacceptable toxicity.

**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 thrombocytosis 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 10^9/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious 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 treatment. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. 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...
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 >50%) 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

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

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

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

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 had 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), 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 x 10⁹/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.1) in Full Prescribing Information]. Patients who have received treatment complete 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), 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 serious 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 course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. Progressive Multifocal Leukoencephalopathy Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [see Adverse Reactions (6.1) in Full Prescribing Information].

Hepatitis B Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. Progressive Multifocal Leukoencephalopathy Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [see Adverse Reactions (6.1) in Full Prescribing Information].

Abbreviations in the Placebo-Controlled Study

Table 3 continued above.

Table 3 continued above.


c *Presented values are worst Grade values regardless of baseline

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

Additional Data from the Placebo-Controlled Study

• 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was 0% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. Clinical Trial Experience in Acute Graft-Versus-Host Disease

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

Table 3: Polychromatia and Nonhematologic Adverse Reactions Occurring in ≥ 15% of Patients in the Double-blind, Placebo-controlled Study During Randomized Treatment

Table 3 continued above.

Table 3 continued above.
### Table 3 continued.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
b Includes dizziness and vertigo
c Includes dizziness and periorbital edema

### 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>Hematology</td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

### 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>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Viral infections</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Diaheaa</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Rash</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

a Selected laboratory abnormalities are listed in Table 6 below
b National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

### 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>Hematology</td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>61</td>
<td>47</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

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

### 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 or with 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.

### Post-treatment Symptom Exacerbation Following Non-melanoma Skin Cancer

In patients starting treatment with 15 mg twice daily (pretreatment Hb ≤ 11.0 g/dL) in patients with MF in two Phase 3 studies. In these two studies, the mean decreases in hemoglobin were 0.97 g/dL at 15 mg twice daily and 1.09 g/dL at 20 mg twice daily. The incidence of Grade ≥ 3 anemia was approximately 6 weeks. One patient (<1%) required temporary discontinuation of Jakafi due to anemia.

### Adverse Reactions to ruxolitinib

In patients with steroid-refractory acute GvHD, 10% of patients treated with Jakafi reported Grade ≥ 3 adverse reactions, with the majority involving blood and the lymphatic system. Table 3 shows the incidence of adverse reactions in patients treated with Jakafi and 7% of patients treated with placebo reported Grade ≥ 3 adverse reactions involving the blood and lymphatic system.

### Hematologic toxicity

The incidence of Grade ≥ 3 anemia was approximately 6 weeks. One patient (<1%) required temporary discontinuation of Jakafi due to anemia.
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FDA APPROVAL INSIGHTS LURBINECTEDIN IN METASTATIC SCLC
Jacob Sands, MD, discusses the June 15, 2020, FDA approval of lurbinectedin (Zepzelca) for adults with metastatic small cell lung cancer (SCLC) and disease progression following platinum-based chemotherapy. The indication, which was based on efficacy data from a phase 2 basket trial (NCT02454972), helps address unmet needs in second-line SCLC for patients with resistant and rapidly progressive disease, Sands said.

FDA APPROVAL INSIGHTS OSIMERTINIB IN EGFR+ NSCLC
Charu Aggarwal, MD, MPH; Lecia V. Sequist, MD, MPH; and Nathan Pennell, MD, PhD, provide perspective on results from the phase 3 ADAURA trial (NCT02511106) and trade insights on potential clinical and financial concerns of using osimertinib (Tagrisso) in the adjuvant setting in patients with EGFR-mutant non–small cell lung cancer (NSCLC).
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PROSTATE CANCER ENTERS A NEW ERA OF PRECISION MEDICINE
With the emergence of molecular biomarkers, prostate cancer has entered a new era, according to Daniel P. Petrylak, MD, who added that DNA repair mutations, prostate-specific membrane antigen, and androgen receptors have been shown to be versatile targets that are beneficial when selecting optimal therapies.
"Prostate cancer is now entering a new era. In lung and breast cancer, we use molecular markers to select treatment. Historically, we were using a one-size-fits-all approach for prostate cancer; however, we now have molecular biomarkers of DNA repair," Petrylak said.
Petrylak, a professor of medicine and urology and coleader of Cancer Signaling Networks at Yale Cancer Center in New Haven, Connecticut, discussed the ever-changing prostate cancer armamentarium, as well as the role of biomarkers and new diagnostic methods in the space.
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ONCLIVE® ON AIR DIZON DISCUSSES ELEMENTS OF SEXUAL HEALTH IN GYNECOLOGIC CANCER
Women who receive a diagnosis of gynecologic cancer may experience issues with body image, and treatment-related toxicities also may negatively affect their quality of life, according to Don S. Dizon, MD. Hear Dizon address the residual psychological effects of gynecologic cancers on women’s sexual health, the challenges of broaching these topics in the clinic, and the role oncologists play in helping patients manage these difficulties.
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**NOTABLE QUOTABLES**

“We have a lot of options that are coming up. It’s really quite exciting to be treating patients with multiple myeloma because now we can tell patients that we have options.”

—Thomas G. Martin, MD

Adult Leukemia and Bone Marrow Transplantation Program; University of California, San Francisco (UCSF)/Helen Diller Family Comprehensive Cancer Center

READ MORE: https://bit.ly/36e7JEt

“My dream has always been to have a precision medicine oncology clinic where, not only would I have the patient’s temperature and blood pressure before entering the room, but I would also have their genomic profile ready and analyzed. We are getting closer to reaching this goal. In other words, I’m getting closer to waking up from that dream, to real-world results. However, more work is needed.”

—Ajjai Shivaram Alva, MBBS

Associate Professor of Internal Medicine
University of Michigan

READ MORE: https://bit.ly/256Z1zw

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**JOURNAL SPOTLIGHT**

**A CONCISE REVIEW OF THE CHANGING LANDSCAPE OF HEPATOCELLULAR CARCINOMA**

Hepatocellular carcinoma (HCC) is the fastest-rising cause of cancer-related deaths in the United States, increasing by 2% to 3% annually, with a 5-year survival rate of 18%. Patients with advanced HCC are at high risk of adverse effects because of baseline hepatic dysfunction, comorbidities associated with chronic liver disease, and potential drug-drug interactions. A review published in the American Journal of Managed Care® discusses recent efficacy and safety data, guideline recommendations, and treatment algorithms for management of HCC.


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**ONCLIVE® VIDEOS**

**RAPID READOUTS**

**FIRST RESULTS FROM CHECKMATE 9ER TRIAL FOR ADVANCED RCC**

Initial results of the phase 3 CheckMate 9ER trial (NCT03141177) demonstrated the efficacy of nivolumab (Opdivo) plus cabozantinib (Cabometyx) versus sunitinib (Sutent) in patients with previously untreated advanced or metastatic renal cell carcinoma (RCC). Rana R. McKay, MD, an associate professor of medicine at the University of California, San Diego, School of Medicine discusses the outcomes of the trial, which met its primary end point of progression-free survival.

WATCH: https://bit.ly/3m3ST86

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**COLEMAN ON THE innovaTV 204 TRIAL IN CERVICAL CANCER**

Findings from the phase 2 innovaTV 204/GOG-3023/ENGOT-cx6 trial (NCT03438396) of tisotumab vedotin in women with previously recurrent or metastatic cervical cancer showed that the novel antibody-drug conjugate elicited a 24% overall response rate with a 7% complete response rate. Ongoing trials are evaluating the agent versus the standard of care for this population. Robert L. Coleman, MD, chief scientific officer of The US Oncology Network and a 2020 Giants of Cancer® award winner, discusses the data’s clinical implications.

WATCH: https://bit.ly/3n13Qso

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**VOKES ON INVESTIGATIVE BIOMARKERS IN RESPONSE TO IMMUNE CHECKPOINT INHIBITORS**

Tumor mutational burden may be the most well-developed molecular biomarker in oncology, according to Natalie Vokes, MD, a medical oncologist fellow at Dana-Farber Cancer Institute in Boston, Massachusetts. By contrast, other biomarkers such as STK11 in lung cancer are not understood as well as the use of driver mutations as biomarkers in this space, including EGFR, ALK, and ROST, is taken for granted, Vokes said.


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New Study Charts Big Drop in Cancer Care

by JESSICA HERGERT

INVESTIGATORS OBSERVED a significant decline in cancer screenings, biopsies, surgeries, office visits, and therapies among senior patients with cancer during the coronavirus disease 2019 (COVID-19) pandemic, according to a study published in JCO Clinical Cancer Informatics.¹

At the pandemic’s early peak in April 2020, screening rates for breast, colon, prostate, and lung cancer were 85%, 75%, 74%, and 56% lower than the baseline rates of the previous year, respectively (FIGURE 1).

Investigators led by Debra Patt, MD, PhD, MBA, found that the most significant reductions in screening occurred in April 2020 versus April 2019. The research team also concluded that billings for some of the most popular treatment agents declined over the same time period.

“When cancer becomes more advanced before it is detected, it becomes a ticking time bomb,” Patt, executive vice president of policy and strategic initiatives at Texas Oncology in Austin and a member of the Community Oncology Alliance (COA) board of directors, said in a news release. “The decrease in screenings, diagnosis, and treatments this year will lead to later-stage cancers for patients, increasing morbidity and mortality for years to come.”

The COVID-19 pandemic has had a profound effect on cancer care throughout the United States. The Centers for Disease Control and Prevention implemented guidelines with the goal of diminishing exposure to the virus. Cancer care facilities across the country implemented stay-at-home orders and short-term treatment adjustments, changed visitation policies, made greater use of telehealth, and delayed surgeries to reduce exposure to medical professionals, patients, and their families.

More than 10 million people in the United States have received a COVID-19 diagnosis and more than 235,000 have died of the disease, according to the Johns Hopkins Coronavirus Resource Center. With the health care system navigating how to best keep elderly and high-risk patients safe, many individuals have experienced decreased access to care, including preventive tests such as cancer screening. Patients with cancer have also reported increased challenges in cancer management visits and surgery.

Although lockdown restrictions have been eased in many areas, investigators do not yet understand the lasting effect of those months on disease progression, cancer morbidity, and cancer mortality. Avalere Health conducted a retrospective analysis on behalf of COA to assess the effect of COVID-19 on the utilization of health services.

Patt and colleagues reviewed data collected from a proprietary provider clearinghouse registry comprised of 5% to 7% of all Medicare Fee-for-Service (FFS) claims submitted from January 1, 2019, to July 31, 2020. CMS claims from institutional and noninstitutional or professional providers were included in the database. In total, 6,227,474 Medicare FFS claims were included in the analysis.

Setting of care was determined using the claim type rather than the site of service modifier to include services delivered via telehealth. This was an important step because CMS finalized additional regulatory and billing flexibilities as a result of the public health emergency.

The data set included claims filed during the first 7 months of each year that were specific to targeted cancer-related services of interest, including diagnostic screening, physician office visits, hospitalizations, surgeries, and infusion therapies administered in the outpatient setting.

Using these data, investigators tracked the number of procedures billed by each rendering provider. They then estimated and compared mean change in volume from 2019 to 2020.

TREATMENTS, HOSPITALIZATIONS: DOWN; USE OF TELEMEDICINE: UP

Billing for the 23 top physician-administered oncology products and their respective biosimilars, including agents such as pegfilgrastim (Neulasta), atezolizumab (Tecentriq), pembrolizumab (Keytruda), nivolumab (Opdivo), and bevacizumab (Avastin), decreased 26% in April 2020 and
fell 31% in July 2020. Similarly, chemotherapy administration services dropped in April, May, and July in both the professional and institutional settings.

Patt et al observed reductions of 71% in breast cancer biopsies, 79% in colon cancer biopsies, and 58% in lung cancer biopsies in April 2020. In July 2020, reductions of 31%, 33%, and 47% were reported, respectively.

Surgical interventions, including mastectomies, colectomies, and prostatectomies, were also consistently down from April 2020 through July 2020.

In April 2020, hospitals reported a 74% reduction in outpatient evaluation and management (EM) visits. New patient visits dropped more compared with established patient EM visits (70% vs 60%). Overall, cancer-related hospitalizations declined 30% in March, 41% in April, 36% in May, 31% in June, and 38% in July.

Although in-office visits were down, patients and practices made greater use of telemedicine. In 2020, use of telemedicine grew every month from March to July compared with 2019. The greatest gain came in April, with practices recording 78,000 more virtual visits compared with the year before.

Despite the uptake of telemedicine, physicians saw fewer patients overall in spring and summer. Including virtual visits, EM visits were down 58% in April; without telehealth, EM visits were down 73%. Nearly all (95%) of telemedicine EM visits were delivered by professional providers from April through July.

“Community oncologists and their team members showed incredible resilience and resolve to deal with this severe crisis by adopting telehealth very quickly, reorganizing workflows, enhancing safety processes at their clinics, and migrating staff to work from home, among other strategies,” study coauthor Lucio Gordan, MD, a medical oncologist at Florida Cancer Specialists in Gainesville, said in a news release. “Although a decrease in services was inevitable, I think the resilience of these practitioners absorbed what could have been a much worse situation.”

The lower rates in screening, EM visits, and administration of anticancer therapies confirmed by the retrospective analysis suggests that patients may present with more advanced disease and higher cancer-related mortality. Furthermore, the disruption in routine cancer screening over the past 6 months could have profound and lasting consequences, according to the study authors.

It is critical to start reassuring elderly and high-risk patients who can seek safe and appropriate care at cancer facilities, the authors said. Additionally, further studies should be conducted to identify the scope of the effect of COVID-19 on specific patient populations.

“We need to detect cancers and stop them before it is too late,” Patt said. “We need to alert all patients that they need to stop medical distancing and get appropriate screening and health care.”

Survey data from 109 health care workers in Europe and the Americas suggest that cancer specialists around the world have turned to telemedicine, according to results presented at the European Society for Medical Oncology Virtual Congress 2020.

“Our survey confirms that COVID-19 has a major impact on organization of patient care and on the well-being of caregivers,” said lead investigator Guy Jerusalem, MD, PhD, of Centre Hospitalier Universitaire de Liège du Sart Tilman in Belgium.

“When you look into the future, the expected problem is the risk of delayed diagnoses of new cancer,” he added. “In our hospitals, we see fewer new patients diagnosed, and the risk is that later we will see more patients with advanced-stage [disease] diagnosed with cancer.”

REFERENCES

FIGURE. Relative Change in Billing Frequencies for Select Cancer Screening Procedures (March-July 2019 vs 2020)1

Billing frequencies were determined by the following procedure codes: breast mammograms (77061, 77062, 77063, 77065, 77066, 77067); colon screening (45330, 81528, 82270, 82272, 82274, G0104, G0105, G0121, G0328); lung screening (31624, G0296, G0297); prostate screening (G0103).
FIVE YEARS AGO, the treatment landscape for multiple myeloma (MM) took a leap forward when, within a 2-week period, the FDA approved the first 2 monoclonal antibodies for the malignancy.1,2 Now, with the development of therapies that target B-cell maturation antigen (BCMA), the field is poised to enter another era of innovation, according to Sagar Lonial, MD. The first new drug directed at BCMA, belantamab mafodotin-blmf (Blenrep), was approved in August,3,4 and other novel agents are advancing through the pipeline.

Lonial, whose work has helped shape the MM field for more than 20 years, played an integral role in those firsts. He served as a leading investigator on the pivotal trials that paved the way for the initial approvals of daratumumab (Darzalex) and elotuzumab (Empliciti) in November 2015 and on the study that led to the FDA’s green light for belantamab mafodotin. In October, Lonial was named a 2020 Giants of Cancer Care® award winner in the myeloma category.

When it comes to BCMA-directed therapies’ potential to change the MM treatment paradigm, Lonial agrees with other experts who say these approaches could be transformative. Strategies directed at BCMA in MM are attractive because the antigen is expressed “much more exclusively on plasma cells,” Lonial said in an interview with OncologyLive®. The result: fewer off-target effects, giving investigators with an opening to further attack the malignancy with a second or third antibody. BCMA, through its ligand, also promotes resistance, he said.

Investigators are examining 3 major strategies for targeting BCMA in MM, Lonial said: antibody-drug conjugates such as belantamab mafodotin, bispecific and T-cell engager antibodies, and chimeric antigen receptor (CAR) T-cell therapies (FIGURE).5 Numerous agents are under study within these categories (TABLE).5

“Blocking BCMA through any of these approaches not only targets the tumor cell, but it also may help to overcome drug resistance,” Lonial said. “Those are really exciting opportunities.”

IDENTIFYING KEY TRENDS
The prospect for innovation in MM is broadly reflected across the spectrum of hematologic malignancies, noted Lonial, who is chief medical officer at Winship Cancer Institute of Emory University in Atlanta, Georgia. He also is professor and chair of the Department of Hematology and Medical Oncology and the Anne and Bernard Gray Family Chair in Cancer, both at Emory University School of Medicine.

He identified 2 key trends driving change: immunotherapy and precision medicine. “I think many of us in the hematologic malignancy field would argue that immunotherapy was first invented in hematologic malignancies, with allogeneic transplant, for instance,” Lonial said. “I think that we have learned to refine that, particularly using cellular therapies such as CAR T cells and ways to augment cellular therapy in all hematologic malignancies.

“I think the second [trend] is really taking the explosion of precision medicine in solid tumor oncology and beginning to apply some of those lessons in hematologic malignancies, as well,” he continued. “We know that in acute leukemia, for instance, we’re now beginning to look at certain mutations and treat them differently. We know that in myeloma, we’re starting to test precision medicine-based approaches, as well. And
we’re using genetics and genomics to identify lymphoma subsets.”

The challenge moving forward involves “marrying the 2 concepts together,” Lonial said. “How do you take both precision medicine and immune therapy and make it sort of a 1-treatment approach for a patient?”

Lonial and other leading experts in hematologic malignancies will tackle the most pressing questions in clinical practice during the 25th Annual International Congress on Hematologic Malignancies*: Focus on Leukemias, Lymphomas, and Myeloma, which will be held as a virtual, interactive conference from February 25 to February 28, 2021. He is cochair of the Physicians’ Education Resource®, LLC (PER®) event.

Also serving as cochairs are Jorge E. Cortes, MD, and Andre H. Goy, MD. Cortes is director of the Georgia Cancer Center in Augusta. Goy is physician in chief of Hackensack Meridian Health Oncology at Hackensack Meridian School of Medicine at Seton Hall University, all in New Jersey, and a professor of medicine at Georgetown University in Washington, DC.

The meeting provides an important opportunity for learning about “moment-to-moment changes” occurring across hematologic cancer types at a time when live meetings are restricted because of the coronavirus disease 2019 pandemic, Lonial said. “These changes are occurring so fast, it’s very hard for the generalist to keep up. And so you get experts, particularly in hematology—which I think is prone to rapid change, and expansion and discovery—in one setting [talking about], what’s newest in lymphoma, what’s newest in leukemia, what’s newest in myeloma, what’s newest in CAR T cells,” he said.

TABLE. Select BCMA-Targeted Therapies in Development for Multiple Myeloma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Development status*</th>
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<tr>
<td><strong>CAR T-cell therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Idecabtagene vicleucel (ide-cel; bb2121)</td>
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<tr>
<td>JNJ-4528 (JNJ-68284528)*</td>
<td>phases 1-3</td>
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<td>CT053</td>
<td>Phases 1 and 1/2</td>
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<td>Phase 1</td>
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<tr>
<td><strong>Antibody-drug conjugates</strong></td>
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<tr>
<td>Belantamab mafodotin-blfm (Blenrep)</td>
<td>FDA approved;</td>
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<tr>
<td>(JNJ-64007957)</td>
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<tr>
<td><strong>Antibodies with dual targets</strong></td>
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<td>CC-93269</td>
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</tr>
</tbody>
</table>

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.

*Information on stages listed on ClinicalTrials.gov website.

**Called ciltacabtagene autoleucel in China.

**MAKING A MARK ON CARE**

In the myeloma field, Lonial is well respected for his research acumen and his leadership skills. He was the lead author on the *Lancet Oncology* paper reporting findings from the SIRIUS trial (NCT01985126), which established a role for daratumumab monotherapy in heavily pretreated patients with refractory MM and led to its first FDA approval. The CD38-directed monoclonal antibody is now a backbone of combination therapy in newly diagnosed and refractory settings.

Lonial also was lead author on the *New England Journal of Medicine* article that detailed the results of the ELOQUENT-2 trial (NCT01239797), which explored elotuzumab in combination with lenalidomide (Revlimid) plus dexamethasone in patients with progressive disease. Based on the findings, the FDA approved the SLAMF7-targeted monoclonal antibody as part of the triplet regimen in patients who have received 1 to 3 prior therapies.

“My involvement with those trials and seeing the positive results is something that I take great pride in because I know how much of an impact each of them can have and is having for patient outcomes,” Lonial said. “Being able to be an integral part of the trials that led to the approval of daratumumab and elotuzumab and bring these immune-based treatments to patients was really a career high point for me.”

S. Vincent Rajkumar, MD, a 2019 Giants of Cancer Care® award winner in the myeloma category, emphasizes that Lonial has made a substantive difference for patients. “He’s been responsible for numerous new drugs coming into the field of myeloma, leading pivotal trials of elotuzumab, daratumumab, belantamab,” said Rajkumar, a consultant and professor at the Mayo Clinic in Rochester, Minnesota. “He’s also changed the paradigm for the treatment of smoldering myeloma by showing in a randomized trial that early therapy with lenalidomide can prolong time to end-organ damage.10

“He’s a great leader,” Rajkumar added. “He’s assembled a huge team at Emory involved in multiple myeloma research, and they have contributed hugely to the field. He’s also a wonderful friend and colleague.”

Similarly, Kenneth C. Anderson, MD, a 2014 Giants of Cancer Care® award winner in myeloma, praised Lonial. “We’ve shared many scientific and personal outings,” said Anderson, program director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics at Dana-Farber Cancer Institute in Boston, Massachusetts. “There’s no one more deserving to be a Giant of Cancer Care.”

Lonial, who has been at Emory since 1997, believes in the power of building a community in patient care and in research. “It’s not just what you do as an individual,” he said. “It’s about creating a team that can magnify and amplify your work even more. I am very fortunate that the team I work with at Emory, at all levels, has coalesced around the common mission of achieving excellence ultimately to improve outcomes. This includes our team in clinic, the program, the department, and the cancer center.

“In myeloma, my future goals are not mine but ours. It’s about creating a team that can achieve goals,” Lonial concluded. “It’s about creating a team that can achieve excellence. I take great pride in because I know how much of an impact each of them can have, and is having, for patient outcomes.”
and beyond is going to be setting and reaching those goals together,” he said.

**TARGETING BCMA**

**Belantamab Mafodotin**

In terms of research goals in the myeloma field, developing drugs that successfully target BCMA has generated intense research interest. Unlike other targets, including CD38 and SLAMF7, BCMA is expressed at significantly higher levels on MM cells and on normal plasma cells but not on other normal tissues.1

Belantamab mafodotin, an antibody-drug conjugate consists of a BCMA-directed antibody covalently linked to a monomethyl auristatin F microtubule inhibitor via a protease-resistant linker. On August 5, 2020, the FDA granted belantamab mafodotin accelerated approval as monotherapy for adults with relapsed/refractory (R/R) MM who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory drug (IMiD).3

The decision was based on overall response rate (ORR) and duration of response (DOR) among 97 patients who received the novel agent at 2.5 mg/kg intravenously once every 3 weeks during the phase 2 DREAMM-2 trial (NCT03525678).11 Patients in the cohort had a median age of 65 years (range, 60-70) and a median 7 lines of prior therapy (range, 3-21); 84% had received more than 4 prior lines.12,13

The ORR was 31% (95% CI, 21%-43%), including 2 patients (2%) with a stringent complete response (sCR), 1 (1%) with a complete response (CR), 15 (15%) with a very good partial response (VGPR), and 12 (12%) with a partial response (PR). After a median follow-up of 6.3 months, the median DOR was not reached.12 Of responders, 73% had a DOR of at least 6 months.11 At the time of data cutoff, median progression-free survival (PFS) was 2.9 months (95% CI, 2.1-3.7) and overall survival data were immature.12

Response rates and median PFS for belantamab mafodotin were comparable to study findings for other MM therapies in the R/R setting, according to Lonial. However, he said, the DOR among responders in DREAMM-2 is noteworthy. “For patients who do respond, the duration of response is 11 months, and I think that’s an important number to put in perspective,” he said. “It speaks to the tolerance of that treatment and the ability for responders to stay on it. That’s why I think it’s such an important step forward.”

In terms of adverse events, belantamab mafodotin’s label includes a boxed warning about the risk of changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, as well as symptoms such as blurred vision and dry eyes. Ophthalmic exams are recommended at baseline, prior to each dose, and for worsening symptoms. The FDA also requires that, because of the risk of ocular toxicity, the drug be dispensed under a risk evaluation and mitigation strategy program.11

“Ocular toxicity is somewhat unique for myeloma drugs,” Lonial said. “It is more of a finding on an exam by an ophthalmologist or an optometrist. It does not always result in significant symptoms. In fact, only 18% to 20% of the time, it actually results in change in visual acuity. And more importantly, partnering with an eye care professional is part of the process.”

Overall, Lonial said, the drug represents “our go-to option for triple-class refractory myeloma.” Confirmatory data needed under the accelerated approval decision may be obtained from the phase 3 DREAMM-3 trial (NCT04162210), which is evaluating belantamab mafodotin monotherapy compared with pomalidomide (Pomalyst) and low-dose dexamethasone in patients with R/R MM who have undergone autologous stem cell transplant (ASCT) or are ineligible for ASCT and have disease progression after 2 or more prior lines of therapy.

Moving forward, Lonial believes belantamab mafodotin has the potential to be used earlier in the treatment time line for MM and combined with other therapies and with immune checkpoint inhibitors. The agent is being tested in combination with bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone in the phase 1 DREAMM-9 trial (NCT04091126) in patients with newly diagnosed MM who are not eligible for ASCT. Ongoing combination studies include the phase 2 DREAMM-4 trial (NCT03848845) pairing belantamab mafodotin with the PD-1 inhibitor pembrolizumab (Keytruda) in R/R MM.

“It does induce immunogenic cell death,” Lonial said. “As such, it’s being tested right now in partnership with, for instance, pembrolizumab, to see whether that immunogenic cell death in combination with a checkpoint inhibitor may actually activate an innate T-cell response separate from the effect directly of the development.”

**Antibodies With Dual Targets**

Lonial said the concept of a bispecific T-cell engager was established in hematologic malignancies with blinatumomab (Blinicyto), a CD19-directed CD3 T-cell engager. The agent is approved for treating patients with B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission and for R/R B-cell precursor ALL. Blinatumomab binds to CD19 on the surface of B cells and to CD3 on the surface of T cells, mediating the formation of a synapse
The future is really exciting, because what I think it suggests is that we can take diseases that are treatable diseases and potentially cure a larger fraction of them,” he said. “The advantage of CARs from my perspective is [that] it is a one-and-done therapy. And if that one-and-done really is done, then it’s a true victory. That opportunity for patients is one that I think we don’t want to limit just to people who are seen in academic centers.”

The agent furthest along in development is idecabtagene vicleucel (ide-cel; bb2121). The FDA is scheduled to decide by March 27, 2021, on a biologics license application for ide-cel as a treatment for patients with MM who have received at least 3 prior therapies, including an IMiD, a proteasome inhibitor, and an anti-CD38 antibody. The application is supported by data from the phase 2 Kar MMA trial (NCT03361748) in heavily pretreated patients (N = 128) with refractory MM. 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 ASCO Virtual Scientific Program. After a median follow-up of 13.3 months across target dose levels, the 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 the median PFS was 8.8 months (95% CI, 5.6-11.6).

Investigators also reported results for orvabtagene autoleucel (orva-cel), a BCMA-directed CAR T-cell therapy, from the phase 1/2 EVOLVE study (NCT03430011) in patients with R/R MM who had undergone at least 3 prior therapies. Among 62 patients treated across 3 dosing levels, the ORR was 92% at a median follow-up of 6.9 months, with a VGPR or better of 68%. Enrollment at the recommended phase 2 dose (600 × 10⁶) is ongoing, and a cohort was recently added for patients who experienced progression following prior BCMA-directed therapy.

Another emerging CAR T-cell therapy in this space is INI-4528, which is being developed under breakthrough therapy designation in the United States and China. Patients with R/R MM who had received at least 3 prior therapies were treated with INI-4528 (called ciltaçabtagene autoleucel in China) in the phase 1b/2 CARTITUDE-1 study (NCT03548207). All 29 (100%) patients dosed during the study demonstrated a response, defined as a PR or better, including a VGPR of 97%, according to updated results presented at the 2020 ASCO Virtual Scientific Program. After a median follow-up of 11.5 months, responses continued in 22 patients.

Lonial is looking forward to seeing how CAR T-cell therapies develop in MM and other malignancies. Community oncologists should keep up with research in this area, he said, because such knowledge will help inform the decision about when to refer a patient to an academic center for cellular therapies, where they are currently available.

“The future is really exciting, because what I think it suggests is that we can take diseases that are treatable diseases and potentially cure a larger fraction of them,” he said. “The advantage of CARs from my perspective is [that] it is a one-and-done therapy. And if that one-and-done really is done, then it’s a true victory. That opportunity for patients is one that I think we don’t want to limit just to people who are seen in academic centers.”

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

Senior editors Jason Harris and Tony Berberabe contributed to this report.
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Enthusiasm Builds for Novel Therapies in Pancreatic Cancer

by CAROLINE SEYMOUR

ALTHOUGH CHEMOTHERAPY remains the benchmark for drug development in pancreatic cancer, signals seen with selective KRAS-targeted agents, PARP inhibitors, and metabolic agents suggest that novel approaches have the ability to prolong survival in the advanced setting, according to Eileen M. O’Reilly, MD.

“It’s exciting times in pancreas cancer. We’re seeing some very interesting science being translated into the clinic,” O’Reilly said in a virtual presentation during the 17th Annual Meeting of the International Society of Gastrointestinal Oncology®, presented by Physicians’ Education Resource®, LLC (PER®). O’Reilly is the Winthrop Rockefeller Endowed Chair in Medical Oncology, codirector of medical initiatives at the David M. Rubenstein Center for Pancreatic Cancer Research, and section head of Hepatopancreaticobiliary & Neuroendocrine Cancers at Memorial Sloan Kettering Cancer Center in New York, New York.

KRAS-TARGETED APPROACHES

Although development of agents aimed at KRAS mutations has been historically challenging, ongoing research suggests that certain molecular subsets, such as KRAS G12C, may be effectively targeted in pancreatic ductal adenocarcinoma (PDAC).

KRAS G12C mutations have been observed in 1% to 2% of patients with pancreatic cancer, O’Reilly said. “It’s a rare subset, but an important subset, and I think we’ll be looking at ways to augment that approach with combination strategies,” said O’Reilly.

For example, data from the phase 1/2 CodeBreak 100 (NCT03600883) trial demonstrated that the KRAS G12C inhibitor sotorasib (AMG 510), a small molecule, demonstrated anticancer activity across several advanced KRAS G12C–mutant solid tumors. Among 12 patients with pancreatic cancer, O’Reilly said. “It’s a rare subset, but an important subset, and I think we’ll be looking at ways to augment that approach with combination strategies,” said O’Reilly.

Another area of interest is the role KRAS mutations may play in therapies aimed in autophagy, a cellular defense mechanism that helps promote resistance to chemotherapy. Investigators are pursuing autophagy inhibitors, the most well known of which is hydroxychloroquine, said O’Reilly.

In findings from a randomized phase 2 trial (NCT01506973), the addition of hydroxychloroquine to gemcitabine plus nab-paclitaxel (Abraxane) failed to improve 1-year overall survival (OS) over the chemotherapy combination alone, at 41% (95% CI, 27%-53%) versus 49% (95% CI, 35%-61%), respectively, in molecularly unselected patients with metastatic pancreatic adenocarcinoma. However, the overall response rate was 38.2% with hydroxychloroquine (n = 55) versus 21.2% with chemotherapy alone (n = 57); all responses were PRs.

After conducting genomic sequencing on samples from 45 participants, investigators found an imbalance between the 2 trial cohorts for KRAS mutations; all patients (n = 21; 100%) in the hydroxychloroquine arm had a mutation compared with 16 of 24 patients (66.7%) in the chemotherapy-alone group. Results of an unplanned analysis showed that progression-free survival (PFS) and OS were prolonged in patients with wild-type KRAS; however, investigators concluded the data set was too limited to draw conclusions.

“We’ll have to see how this pans out with more potent inhibitors of autophagy in other contexts in pancreas cancer,” O’Reilly said.

Another strategy involves antisense inhibition with small interfering RNA (siRNA) targeting KRAS G12D and G12. The
Providing an anecdotal example of the potential for such targeted strategies, O’Reilly shared the case of a patient with an NRG1 fusion and KRAS wild-type PDAC who achieved a sustained antitumor response and a marked reduction in cancer antigen 19-9 after receiving zenocutuzumab (MCLA-128), a dual HER2/HER3 inhibitor.

O’Reilly noted that afatinib (Gilotrif), a pan-HER inhibitor, and other HER2/3 inhibitors are being evaluated in pancreatic cancer.

**PARP INHIBITION**

Germline testing with a multigene panel is recommended for all patients with PDAC, and tumor and somatic profiling is recommended for all patients with locally advanced or metastatic disease who are candidates for anticancer therapy, said O’Reilly.

Overall, approximately 26% of patients with pancreatic cancer have mutations for which therapies have been identified (FIGURE). Although the rate of actionable mutations in practice represents the minority of patients, taking the time to test these patients can lead to drastically improved survival. In a retrospective analysis, investigators found that patients who were matched with targeted therapy for their genomic alteration (n = 46) experienced a doubling of OS versus those who went unmatched, at 2.58 years versus 1.51 years, respectively (HR, 0.42; P = .0004).

Moreover, data from the phase 3 POLO trial (NCT02184195) have reinforced the importance of tumor testing in practice, explained O’Reilly. In December 2019, the FDA approved olaparib (Lynparza) for the maintenance treatment of patients with germline BRCA1-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen, based on the POLO findings. In the trial, 154 patients who had a germline BRCA1/2 mutation were randomized 3:2 to receive olaparib tablets at 300 mg twice daily as maintenance therapy (n = 92) versus placebo, also twice daily (n = 62).

The median PFS was 7.4 months (95% CI, 4.1-11.0) with olaparib versus 3.8 months (95% CI, 3.5-4.9) with placebo (HR, 0.53; 95% CI, 0.35-0.81; P = .0035). An interim analysis of OS at data maturity of 46% demonstrated no difference between arms, with a median OS of 18.9 months (95% CI, 14.9-26.2) with olaparib versus 18.1 months (95% CI, 12.6-26.1) with placebo (HR, 0.91; 95% CI, 0.56-1.46; P = .683). A final OS analysis is expected in 2021 once 106 deaths have occurred out of 154 patients, O’Reilly said.

A number of studies are underway, seeking to build on the proof of principle from the POLO study, O’Reilly said. These include studies evaluating whether the addition of a checkpoint inhibitor to a PARP inhibitor can lead to improved outcomes following platinum-based therapy.

**METABOLIC AGENTS**

Another area of exploration in pancreatic cancer involves the development of agents that target metabolic processes. Devimistat (CPI-613) is currently under investigation in the phase 3 AVENGER 500 trial (NCT03504423) as frontline therapy for patients with metastatic pancreatic adenocarcinoma. Patients are being randomized to 500 mg/m² of devimistat plus modified FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) or standard FOLFIRINOX. The experimental drug will be administered on days 1 and 3 of each cycle (14 days), and chemotherapy will be given to participants in both arms from day 1 to 3 of each cycle.

“The trial has completed enrollment based on an interesting signal in a phase 1b trial. [Devimistat] interferes with the tricarboxylic acid cycle and has direct antimitochondrial effect. It’s also building on
FOLFIRINOX and is one of the few studies that does so with regard to novel therapeutics in pancreas cancer,” said O’Reilly.

Eryaspase is another agent that falls under the umbrella of investigational metabolic therapies in pancreatic cancer, O’Reilly said. The agent, an asparaginase inhibitor, “is encapsulated in red blood cells and given as an infusion,” she said.

The therapy demonstrated statistically significant improvements in OS and PFS in combination with chemotherapy as second-line treatment of patients with advanced pancreatic adenocarcinoma in a phase 2b trial (NCT02195180). Patients were randomized 2:1 to receive either eryaspase in combination with gemcitabine or modified FOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) or to gemcitabine or modified FOLFOX6 alone.

The experimental combination resulted in median OS of 6.0 months (95% CI, 4.8-6.6) versus 4.4 months (95% CI, 3.0-5.0), which translated into a 40% reduction in the risk of progression or death (HR, 0.60; 95% CI, 0.41-0.87; \( P = .008 \)) The median PFS was 2.0 months (95% CI, 1.8-3.4) in the erysaspe arm versus 1.6 months (95% CI, 1.4-1.8) in the chemotherapy-alone group (HR, 0.56; 95% CI, 0.37-0.84; \( P = .005 \)).

In April 2020, the FDA granted a fast-track designation to erysaspe for the treatment of patients with metastatic pancreatic cancer in the second-line setting. The ongoing phase 3 Trybeca-1 trial (NCT03665441) is evaluating the agent in combination with chemotherapy versus chemotherapy alone in the second-line setting.²

With regard to immunotherapy, pancreatic cancer is the prototypic disease for a highly immunosuppressed environment, said O’Reilly. Single-agent checkpoint inhibitors have no role to play in pancreatic cancer, apart from perhaps in patients with microsatellite instability-high or mismatch repair–deficient tumors, and even combination strategies with or without chemotherapy have been unable to show a robust benefit in survival.

“We know we can reproducibly alter the microenvironment, but it remains to be seen whether that can be converted into a clinically meaningful signal,” concluded O’Reilly. ³

MOLECULAR PROFILING HAS LED to a better understanding of biliary tract cancers (BTC) by revealing new markers that can be targeted by novel therapies, according to Milind Javle, MD. Immunotherapy also is a promising area of research, but predictive biomarkers remain elusive, he said.¹

Although immunotherapy is becoming a dominant modality in many cancers, targeted agents “have made remarkable progress in BTC,” said Javle, a professor of gastrointestinal medical oncology at The University of Texas MD Anderson Cancer Center in Houston. “[Study findings have demonstrated] that the genetic profiles of intrahepatic cholangiocarcinoma [CCA], extrahepatic cholangiocarcinoma, and gallbladder cancers are diverse; in fact, 50% of patients have actionable mutations such as \( \text{FGFR, IDH1, HER2, and BRAF} \).”

The mutational picture varies among subsets of BTCs, Javle and colleagues found in an analysis of tumors from 554 patients. The number of genomic alterations per patient was 3.6 for intrahepatic CCAs, 4.4 for extrahepatic CCAs, and 4.0 for gallbladder carcinomas (FIGURE).²

Javle discussed several classes of novel therapeutics that have shown promising responses with BTC during a presentation at the 17th Annual Meeting of the International Society of Gastrointestinal Oncology⁴.

**IDH1 INHIBITORS IN IDH1+ CCA** In the global, phase 3, randomized, double-blind ClarIDHy trial (NCT02989857), investigators examined the use of the IDH1 inhibitor ivosidenib (Tibsovo) versus placebo in the second-line treatment of patients with advanced IDH1-mutant CCA; crossover was permitted.³ The agent currently is approved in acute myeloid leukemia settings.

The study met its primary end point of median progression-free survival (PFS). Results showed a median PFS of 2.7 months in the ivosidenib arm versus 1.4 months (95% CI, 1.6-4.2) in the placebo arm (HR, 0.37; CI, 0.25-0.54; 1-sided \( P < .001 \)). The 6-month PFS rate was 32% in the ivosidenib arm versus not evaluable (NE) with placebo; the 12-month PFS rates were 22% and NE, respectively. Additionally, the disease control rate (DCR), comprising partial response (PR) and stable disease (SD), was 53% in the ivosidenib arm (2% PR, 51% SD) and 28% in the placebo arm (0% PR, 28% SD).

The median overall survival (OS) in the intent-to-treat population was 10.8 months (95% CI, 7.7-17.6) in patients who were treated with ivosidenib and 9.7 months (95% CI, 4.8-12.1) in those who received placebo (HR, 0.69; 95% CI, 0.44-1.10; \( P = .06 \)). The 6- and 12-month OS rates in the ivosidenib arm were 67% and 48%, respectively; these rates were 59% and 38% in the placebo arm, respectively. Final OS data from the trial showed that although there was a trend for improved OS in those who received the IDH1 inhibitor compared with placebo, it was not statistically significant.⁴

“[ClarIDHy] has led to studies of IDH resistance. [One study] demonstrated in serial biopsies that there’s isoform switching, whereas a percentage of patients who had IDH1 mutations and resistance [may switch] to an IDH2 isoform, which will, perhaps, be targetable,” Javle explained. “However, at the current time, IDH2 targeting remains experimental.”

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Targeted Agents Show Promise in Biliary Tract Cancers

**by HAYLEY VIRGIL**

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FGFR INHIBITORS IN CCA

Approximately 15% of CCA cases, particularly intrahepatic CCA, have mutations in the FGFR pathway, and these mutations are activating; they unleash a downstream cascade of proliferative and resistance mechanisms that can be targeted with small molecule inhibitors, explained Javle.

Patients whose tumors harbor these mutations are often younger, under the age of 40 years. These mutations are also found to be more common in Caucasian patients than in Asian patients, for example, and there is a distinct pattern of concurrent mutations. Several FGFR inhibitors have been investigated in many other tumor types, including infgratinib, ponatinib (Iclusig), and pemigatinib (Pemazyre), which are being examined in the FGFR pathway, and these mutations are found in 5% of CCA tumors, there is still a need for effective therapies following patient progression on a gemcitabine-based chemotherapy. Since dabrafenib (Tafinlar) and trametinib (Mekinist) have shown activity in multiple FGFR V600E-mutated tumor types, the safety and efficacy of the combination was evaluated in patients with BTC in the phase 2 ROAR study (NCT02034110).7

Patients who received the combination therapy (n = 43) experienced an investigator-assessed ORR of 51% (95% CI, 36%-67%). The independent reviewer-assessed ORR was 47% (95% CI, 31%-62%). The study showed a need for more routine testing to identify BRAF V600E mutations in patients with BTC, noted Javle.

“This is quite similar to the data seen in BRAF V600E-mutated malignant melanoma,” Javle said. “Clearly, at this point, every patient who has a BRAF mutation will probably have access to a BRAF plus MEK inhibitor—in this study, dabrafenib plus trametinib was examined. This has made it into the National Comprehensive Cancer Network guidelines.”

ADDITIONAL PATHWAYS

Several other pathways are under investigation in clinical trials. For example, in a phase 2 trial (NCT02711553), 309 patients with untreated advanced or metastatic BTC received frontline treatment for up to 8 cycles with the VEGFR2 inhibitor ramucirumab (Cyramza) in combination with gemcitabine plus cisplatin (n = 106, intravenous [IV]), the MET multikinase inhibitor merestinib (LY2801653) plus gemcitabine/cisplatin (n = 102, oral), or placebo plus gemcitabine/cisplatin (n = 52, IV; n = 49, oral).8

Results showed that patients who were given the ramucirumab regimen experienced a median PFS of 6.47 months (95% CI, 5.65-7.13) and a median OS of 10.45 months (95% CI, 8.48-11.86). Those in the merestinib arm had a median PFS of 6.97 months (95% CI, 6.21-7.13) and a median OS of 14.03 months (11.96-16.36). Neither of the experimental arms was found to vastly improve OS or PFS over the placebo regimen, which had a median PFS of 6.64 (95% CI, 5.59-6.83) and a median OS of 13.04 months (95% CI, 11.40-15.31).

Investigators are also examining olaparib (Lynparza) and other PARP inhibitors in patients with BRCA1/2 and DNA damage repair mutations. Additionally, they are evaluating PI3K inhibitors and ATP inhibitors including copanlisib (Aliqopa) in those who are positive for PIK3CA and AKT mutations, and testing porcupine inhibitors in patients with RSPO fusions and RNF43 mutations, said Javle.

Moreover, an ongoing phase 2 trial is assessing the ALK inhibitor crizotinib (Xalkori; NCT02034981) in advanced CCA and other gastrointestinal malignancies.9

For a full list of references, see the article at https://bit.ly/2TxujR2.
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Next-Generation Endocrine Therapy Moves Forward in Breast Cancer Trial

by DENISE MYSHKO

AMCENESTRANT (SAR439859), A NEW oral form of endocrine therapy that has shown early signs of efficacy, is being evaluated against the current standards of care in patients with estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer.

The agent, a selective estrogen receptor degrader (SERD), is being compared with physician’s choice of endocrine therapy in the open label, phase 2 trial AMEERA-3 trial (NCT04059484). The control treatment involves choosing monotherapy from a list of agents with different mechanisms of action: anastrozole, letrozole, or exemestane, which are aromatase inhibitors; tamoxifen, a selective estrogen receptor modulator; or fulvestrant (Faslodex), a SERD (FIGURE).

Amcenestrant is a next-generation SERD that, in preclinical studies, has demonstrated antitumor efficacy and regression in ER-positive breast cancer models and can be administered as an oral therapy because of its favorable pharmacokinetic profile. Fulvestrant, which has been available since 2002, must be administered via intramuscular injection because of limitations including low solubility and weak permeation.

"It’s exciting to have a potential SERD that is oral and has potentially better bioavailability than fulvestrant. So many of us wondered whether these [novel] agents could substitute for fulvestrant in the future and potentially be a better option," said Sara M. Tolaney, MD, MPH, principal investigator for the AMEERA-3 trial, in an interview with OncologyLive®.

SERDs work by serving as competitive antagonists to the ER, inducing conformational changes that lead to degradation of the receptors. "They have dual functions. I think this accounts for their ability to block the signaling in ER-dependent tumors that may be potentially resistant to other endocrine therapies," said Tolaney, who is associate director of the Susan F. Smith Center for Women's Cancers and director of Clinical Trials in Breast Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts.

"Amcenestrant has shown activity in patients regardless of ESR1 mutation status, which makes it very intriguing," added Tolaney, who also is an associate professor of medicine at Harvard Medical School in Boston. "It is blocking the estradiol and binding to the estrogen receptor, which promotes inactivation and degradation. It’s thought to do so more potently than fulvestrant does."

AMEERA-3 STUDY DETAILS

The goal of AMEERA-3 is to demonstrate that amcenestrant is superior to the endocrine therapy of physician’s choice in patients who are refractory to endocrine therapy and have metastatic hormone receptor (HR)-positive breast cancer, Tolaney said. The primary end point is progression-free survival (PFS). Secondary end points include overall survival (OS), objective response rate (ORR), disease control rate, clinical benefit rate (CBR), and duration of response (DOR).

Tolaney said the trial design takes into account the options available to patients with HR-driven breast cancer. "In the first-line setting for metastatic hormonal receptor–positive disease, patients get a different endocrine backbone. Some patients are getting an aromatase inhibitor with CDK4/6 inhibition; some are getting fulvestrant with CDK4/6 inhibition. This trial allows for the flexibility for the physician to choose what is most appropriate for the patient based on their prior exposure to endocrine treatment," Tolaney said.

Amcenestrant is being administered at 400 mg daily in 28-day cycles until unacceptable toxicity, progression, death, investigator decision, or patient request.
The comparators are being given based on approved labeling. In terms of eligibility requirements, the trial limits participants to 1 prior targeted therapy with a CDK4/6 inhibitor or 1 prior treatment with chemotherapy for advanced or metastatic disease. The criteria also require patients outside of China to receive a prior CDK4/6 inhibitor if they can get reimbursed for it; the number of participants without previous CDK4/6 inhibitor therapy will be capped at 20%. “It has become standard of care to use CDK4/6 inhibitors with endocrine treatment in the first-line setting for metastatic, hormone receptor-positive disease,” Tolaney noted.

Additionally, eligible patients are required to have progressed after 6 or more months of continuous endocrine therapy for advanced disease or to have relapsed while on adjuvant endocrine treatment for 2 or more years or within 12 months of receiving that therapy. Patients with brain metastases are excluded, as well those who previously received an mTOR inhibitor or a SERD other than fulvestrant, which must be stopped at least 3 months before randomization.

The trial seeks to enroll 282 patients through 126 worldwide locations. An extension is planned with an additional 90 Chinese participants expected to be enrolled. Tolaney said the trial is more than halfway accrued. “It was a little delayed because of COVID [coronavirus disease 2019], but it has been doing well otherwise,” she said. She anticipates enrollment will be completed early in 2021.

**EARLY CLINICAL EFFICACY**

The rationale for AMEERA-3 stems from findings from an ongoing first-in-human phase 1/2 study (NCT03284957) testing amcenestrant as monotherapy and in combination with other agents in post-menopausal women with ER-positive, HER2-negative metastatic breast cancer.

Investigators presented results for patients who received amcenestrant monotherapy in 2 cohorts of the study at the 2020 American Society of Clinical Oncology Virtual Scientific Program. The pooled data included women who received from 150 mg to 600 mg daily in part A of the study and those who took 400 mg daily in part B of the study. The primary end point in part B was ORR, documented by RECIST v1.1 criteria; secondary end points included overall safety profile; ORR based on ESR1 status (mutated or wild type); and CBR defined as complete and partial responses plus stable disease for 24 weeks or more.

All patients in the study (N = 62) had received prior endocrine therapy in the advanced setting; 48.4% had 3 or more previous lines of therapy. Among 59 evaluable patients, the ORR was 6.8% (90% CI, 2.3%-14.8%), all partial responses. The CBR was 35.6% (90% CI, 25.1%-47.1%), which study investigators said was similar to that of fulvestrant in less heavily pretreated patients. Patients with wild-type ESR1 (n = 30) had better responses than those with mutant ESR1 (n = 28) for ORR (10.0% vs 3.6%, respectively) and CBR (40.0% vs 32.1%).

In a subset of women without prior treatment with a SERD, CDK4/6 inhibitor, or mTOR inhibitor (n = 14), the antitumor activity of amcenestrant was substantially greater and compared favorably with historical results for fulvestrant. The ORR was 21.4% (90% CI, 6.1%-46.6%) and the CBR was 64.3% (90% CI, 39.0%-84.7%).

Amcenestrant had a favorable safety profile with limited treatment-related adverse effects (TRAEs); 61.3% of women in the study had adverse effects, and all were grade 1 or 2, most commonly hot flush (16.1%); constipation (9.7%); and arthralgia (9.7); decreased appetite, vomiting, diarrhea, nausea and decreased appetite (all 8.1%); and fatigue (6.5%). No patients discontinued because of TRAEs.

**FUTURE DIRECTIONS**

Amcenestrant has the potential to become the “best-in-class endocrine backbone across treatment lines in HR-positive breast cancer,” according to Paul Hudson, chief executive officer of Sanofi, the company developing the drug.

Amcenestrant also is being evaluated in comparison with letrozole in an ongoing phase 2 “window of opportunity” study (NCT04191382) in newly diagnosed ER-positive, HER2-negative breast cancer. In this study, patients are being randomized to receive amcenestrant at 400 mg or 200 mg daily, or to receive letrozole at 2.5 mg daily for 14 days prior to surgery. Biopsies will be taken before and after therapy to assess tumor biomarkers.

The primary end point is a change in Ki-67 after a 14-treatment period compared with baselines levels via immunohistochemistry assessment in tumor tissue. Secondary end points include the proportion of patients with relative decrease from baseline in Ki-67 of 50% or more, change in ER expression compared with baseline, and safety and tolerability. Ki-67 is a biomarker of cellular proliferation, and expression of Ki-67 in 14% or more of tumor nuclei is associated with poor prognosis in early breast cancer, investigators noted. This study began enrolling patients in December 2019 and is being conducted at 16 sites worldwide.

Another study, AMEERA-5 (NCT04478266), is testing amcenestrant in combination with palbociclib (Ibrance), a CDK4/6 inhibitor, versus letrozole plus palbociclib as a first-line therapy for patients with ER-positive, HER2-negative breast cancer. The study, which aims to recruit 810 patients, has a primary end point of PFS and secondary end points of OS, ORR, DOR, and CBR.

Additionally, the Quantum Leap Healthcare Collaborative announced in June 2020 that amcenestrant was selected to be part of a new I-SPY 2 study arm. The study, known as the I-SPY 2 Endocrine Optimization Protocol (EOP), is focused on patients with molecularly low-risk, clinically high-risk, HR-positive, HER2-negative clinical stage II or III invasive breast cancer. Amcenestrant will be tested as a monotherapy and in combination with up to 3 other agents.

The I-SPY program was designed to identify therapies that are most effective in specific patient subgroups based on biomarker signatures. Sanofi is supplying the drug and providing financial support.
Choueiri Highlights Promising Cabozantinib Combos in RCC

by BRITTANY COTE

NOVEL DOUBLET AND TRIPLET REGIMENS that combine cabozantinib (Cabometyx) with checkpoint blockade immunotherapy are starting to emerge as potential new frontline standards for patients with advanced or metastatic renal cell carcinoma (RCC), according to Toni Choueiri, MD.

In the phase 3 CheckMate 9ER study (NCT03141177), the combination of cabozantinib and the PD-1 inhibitor nivolumab (Opdivo) proved superior to single-agent sunitinib (Sutent) in patients with previously untreated disease, according to data that Choueiri presented during the European Society for Medical Oncology Virtual Congress 2020.

At a median follow-up of 18.1 months, a median progression-free survival (PFS) was 16.6 months (95% CI, 12.5-24.0) with the combination compared with 8.3 months (95% CI, 7.0-9.7) for sunitinib (HR, 0.51; 95% CI, 0.41-0.64; CI, 7.0-9.7) for sunitinib (HR, 0.51; 95% CI,

Q Was the regimen well tolerated?
A The AEs [adverse effects] were manageable. A higher incidence of liver function test abnormalities was observed in the combination [arm]; however, [the number of] deaths from [treatment] were similar on both [arms]. Treatment discontinuation due to AEs were low in both arms. Three percent [of patients on the] combination arm discontinued treatment of both drugs versus 8.8% on the sunitinib [arm].

Q What was noteworthy about the CheckMate 9ER findings?
A Beyond any reason of a doubt, the combination resulted in a significant major clinical benefit over the control arm of sunitinib. The primary end point of PFS was doubled, going from 8.3 months to 16.6 months; this was highly statistically significant. OS was also prolonged, and the risk of death was reduced by 40%. Responses went from 27% to 56% on BICR.

Q What did results reveal with regard to quality of life?
A One of the interesting things in this study were the QOL metrics. We don’t just want the patient to live longer; we also want them to feel better. We used the Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19), which involves 19 questions, and a subset of FKSI-disease-related symptoms, which includes 6 questions. Patients filled out the questionnaire at baseline, during their visits, and during follow-up in both arms. At the vast majority of the time points, we saw a statistical significance favoring the combination of cabozantinib/nivolumab over sunitinib in terms of QOL.

Q What are the next steps for cabozantinib/nivolumab?
A We are moving forward and [accruing] patients to another ongoing phase 3 trial, COSMIC-313; this trial is examining nivolumab plus ipilimumab versus the combination comprised of nivolumab, ipilimumab, and cabozantinib.

Similarly, DIGREE [NCT03793166] is a [phase 3] study that involves the 3 drugs but they are being given in a different sequence. First, patients are given nivolumab/ipilimumab and if they achieve a complete response [CR], they could stop [treatment] after 1 year. If a patient has disease progression, they could be switched to cabozantinib. The 70% of patients who do not have progressive disease and do not have a CR will get randomized to nivolumab maintenance, which is what we do normally with nivolumab/ipilimumab or nivolumab/cabozantinib.
Watch Now For Clinical Insights About GAVRETO™

**INDICATION**

GAVRETO® is a kinase inhibitor 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 trial(s).

**JOIN THE EXPERTS:**

**Eric H. Bernicker, MD**
Associate Professor of Clinical Medicine, Weill Cornell Medical College
Houston Methodist Cancer Center

**Viola Zhu, MD, PhD**
Associate Clinical Professor of Medicine

**In this iPub®, Dr. Bernicker and Dr. Zhu will:**

- Explore the data from GAVRETO clinical trial
- Review important safety information of GAVRETO
- Present a hypothetical patient case from identification to management

**IMPORTANT SAFETY INFORMATION**

**Pneumonitis** occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4 and 0.6% 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 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 17 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 2.57% 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 females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. 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.

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

Please see Brief Summary of full Prescribing Information on adjacent pages.
INDICATIONS AND USAGE
GAVRETO is indicated for the treatment of adult patients with metastatic 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 trial(s).

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. 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 ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension
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 for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5.4% and increased ALT occurred in 46% of patients, including Grade 3 or 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.

Hemorrhagic Events
Serious, including fatal, hemorrhagic events can occur with GAVRETO. 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.

Risk of Impaired Wound Healing
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.

Embryo-Fetal Toxicity
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.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

ADVERSE REACTIONS
The following clinically significant 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 creatinine 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 dosage 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 jiroveci pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal

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><strong>Chemistry</strong></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><strong>Hematology</strong></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 toxicology 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 toxicology 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.
Infrastructure of Oncology Care Model Helps Practices Through COVID-19

by MARY CAFFREY

NOTHING ABOUT TAKING CARE of patients with cancer during the coronavirus disease 2019 (COVID-19) pandemic has been easy, but those practices that had already embraced transformation under the Oncology Care Model (OCM) are finding that its monthly payments and other features offer stability during an unprecedented health emergency.

That’s what Alexandra Chong, PhD, lead for the OCM within the Center for Medicare and Medicaid Innovation (CMMI), told the hundreds of online attendees at the 9th annual meeting of Patient-Centered Oncology Care®, presented virtually on September 25, 2020, by the American Journal of Managed Care®. The meeting engaged leaders from the payer, academic, and patient advocacy communities to discuss issues on patient-centered oncology care.

“We are living in a totally different world,” said event cochair Kashyap Patel, MD, CEO of Carolina Blood and Cancer Care Associates of Rock Hill, South Carolina, as he introduced Chong. “What we are learning is how COVID-19 impacts not just us as [to] what we do in the office, but how it impacts the rapid adaptation and changes from the payer perspective.”

Chong spent much of her talk walking attendees through the fine points of the OCM, which had been poised to transition toward Oncology Care First (OCF), a next-generation model built on a bundled-payment framework instead of fee for service (FFS).

As Chong explained, due to COVID-19, the OCM has been extended another year through 2022, and the CMMI has not yet fleshed out the details of OCF. OCM is an episode-based model, Chong said, that attaches 2 reimbursement elements to each practice’s commitment to reach certain financial and quality benchmarks while meeting practice standards that include having 24/7 access to medical records and developing care and survivorship plans with patient input. Although the number of practices in the OCM is 138, the number of physicians involved exceeds 7000, and the model now reaches 150,000 Medicare patients each year, or about a quarter of all FFS beneficiaries.

Practices in the OCM receive $168 per patient per month in Monthly Enhanced Oncology Services (MEOS) for delivering this higher-level care, as well as Performance-based Payments (PP), which come after each 6-month evaluation period ends.

As Chong explained, the work practices undertook to redesign their business for the high-touch requirements of the OCM was not easy—and it was a learning process for both sides.

But it’s paying dividends now. Practices that rely on administering expensive therapies—and having new patients walk through the door—have seen revenue plummet as people skip cancer screenings.

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Alexandra Chong, PhD

For more from the American Journal of Managed Care®, visit https://bit.ly/2IaS9Qv
Those in the OCM have had some lifelines extended to them. “We decided to retain the billing and keep up those MEOS payments, because we have heard across all of our practices, or majority of our practices, that a lot of the infrastructure that was put into place for the implementation of OCM has really helped our practices in terms of still achieving or still… focusing their care on their beneficiaries,” Chong said.

To be sure, the OCM is not perfect, and Chong said the CMMI has heard the message from participating physicians that it must rethink reporting requirements and turnaround performance data in a time frame that lets practices fiX problems quickly.

Because of COVID-19, the CMMI has made some data reporting requirements optional during the Public Health Emergency, including aggregate quality measure reporting and beneficiary-level clinical and staging data reporting.

“A majority of our practices still reported on these data, even though it was optional,” Chong noted.

Before COVID-19 hit, according to Chong, the OCM was gaining momentum as it headed into its final year. A third of the practices in the model had agreed to take on 2-sided risk or “some type of downside risk,” she said.

By embracing the tools that make the OCM work, Chong continued, “Participants have been able to not lose that momentum in providing the high-quality care that they had committed to giving their beneficiaries.”

**FROM THE OCM TO THE OCF**

Patel led a panel discussion on shifting from the OCM to the OCF, which featured Aaron Lyss, director of strategic payer relations, OneOncology; Terrill Jordan, president and CEO, Regional Cancer Care Associates; Mariam Alboustani, manager, Pharmacy Services, Blue Cross Blue Shield of Michigan; and Randall A. Oyer, MD, Lancaster Cancer Center/Penn Medicine.

Patel likened the OCM to an architect’s blueprint of how cancer care should work, one into which participants have put time and resources to build. He launched the panel discussion by asking what the OCF should look like when fully presented.

Jordan said the ground has shifted with COVID-19 and the CMMI must acknowledge that the population that comes through the door post pandemic will be different. “We will have to think about that, and challenge CMS/CMMI to take that into account appropriately,” he said.

The CMMI had a brief stakeholders’ meeting November 4, 2019, to discuss its OCF outline, Patel said, but there has been little information forthcoming since then. Oyer said the concerns among practices remain: physicians worry about improving outcomes, decreasing administrative burden, and maintaining revenue.

“We are also concerned about what our patients are facing, making access available to people across our entire community, [and] providing quality outcomes and patient experience. And then we’re all concerned about our organizations—we work in these organizations.”

In terms of financial stability at the practice level, he said, it’s hard to deliver good care and be a community resource. Doing things the right way depends on having the resources to build a good team, Oyer said.

“One of the really good things that came out of OCM for us was that everybody on the team understood their value.”

Like Jordan, Oyer values transparency. “People see a line of sight between what they do in their daily practice and what results they want to accomplish.”

Lyss noted that achieving buy-in throughout an organization was important for success in the OCM and will be even more so in the OCF. The challenges ahead only become surmountable, he said, “through a culture throughout the organization that is committed to value and that is committed to evolve, adapting to change.”

Practice transformation “is going to take time. It’s going to be really hard; there are no shortcuts,” he continued.

Alboustani said her payer is working with practices on the data-sharing challenges of the OCM, but that success in shifting to value-based care is not just about an individual model, it’s about recognizing that value-based care is not going away. “It’s not a phase. It’s probably going to become the norm down the line—and we all have to collaborate. We all have to work better in making this efficient for everyone—for the patient, for the plan, and for the provider.”

As practice transformation evolves, so must the concept of shared savings, Jordan said. Practices cannot keep squeezing savings out of the practice of oncology, and it’s a reason why some have left the OCM even as they embrace its transformation principles.

“The idea that you’re essentially judged against or measured against your own historic performance, I think is a real problem,” he said. “You should get measured against the market that you’re in. The variability in those markets is significant.”

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9 Ways to Achieve Financial Security

by DAVID J. SCHILLER

ONCOLOGISTS CAN MAXIMIZE their financial position and create security throughout their work life and retirement. Staying in shape financially is easier than making mistakes and then attempting to fix them. Here are 9 ways to achieve your financial goals.

1. **Start funding a Roth IRA.** The annual limit is $6000. The principal and interest will grow tax-free (not tax-deferred) over decades. At retirement, you could have $500,000 (invested at historic rates of growth).

2. **Contribute to your employer’s retirement plan.** Begin the day you are eligible, at the rate of at least 5% of compensation. At age 35, increase your contribution to 10% of compensation up to the legal maximum. Do not borrow from your 401(k).

3. **Avoid bad debt.** Mortgages, student loans, and car payments should be minimized or eliminated as quickly as possible so that available income can be used for investment. Purchase cars instead of leasing. Avoid credit card debt, which means you are spending money before you earn it.

4. **Use tax-advantaged investment vehicles.** Make sure you are using tax-advantaged investment vehicles. Interest income on your investments is taxed at ordinary income rates, but dividends issued from stock or mutual funds are taxed at lower, long-term capital gains rates.

5. **Consider no-load mutual funds.** When investing in the stock market, consider no-load mutual funds that do not require an investment adviser. (A “load” is the fee or commission paid to your salesperson.)

6. **Make a budget and stick to it.** Develop a budget, first allocating funds to long-term savings such as a retirement plan, then to short-term savings, then to unavoidable recurring costs such as rent or mortgage, loans, food, and discretionary expenditures.

7. **Fund a 529 plan.** You can fund a 529 plan for education expenses for your children. If you don’t have children yet, name yourself as the beneficiary and then change it after your children are born.

8. **Don’t put off writing your will.** It is imperative to have a will so that your wishes are implemented. Many tax advantages are available when bequeathing assets to heirs that don’t require complicated trusts. Maintain an up-to-date will.

9. **Protect your ability to earn income.** Your most valuable asset is your income stream over the coming years. Protect it with private disability and life insurance policies.

David J. Schiller, Esquire, is a physician contract and tax attorney and has practiced in Norristown, Pennsylvania, for the past 30 years.
New Strategies Enhance Care in mUC

by GURU P. SONPAVDE, MD

ALTHOUGH METASTATIC UROTHELIAL CARCINOMA (mUC) remains generally incurable, management of bladder cancer has witnessed several multidisciplinary advances in the past few years (FIGURE). Cisplatin-based combination chemotherapy employing gemcitabine plus cisplatin; methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) or dose-dense MVAC yields a median survival of 14 to 15 months and a 3-year overall survival (OS) of 5% to 15%, suggesting some potential cures.1

Informed by tumor biology, the therapeutic landscape for mUC has been transformed with the advent of the PD-1/PD-L1 inhibitors pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo), durvalumab (Imfinzi), and avelumab (Bavencio) for the treatment of patients with progressive disease who have previously received platinum-containing regimens.2

In results from the KEYNOTE-045 trial (NCT02256436), pembrolizumab induced an impressive 2-year OS rate of 26.9% compared with 14.3% with taxane or vinflunine chemotherapy in the intention-to-treat (ITT) population regardless of PD-L1 expression.3 While the objective response rate (ORR) was higher with pembrolizumab (21.1% vs 11.0%), the most impressive aspect of outcomes may be the prolonged median duration of response greater than 2 years compared with just 4.4 months with chemotherapy. Pembrolizumab and atezolizumab are also approved as first-line therapy for platinum-ineligible patients and cisplatin-ineligible patients with high tumor PD-L1 expression, although phase 3 trials have not demonstrated improved survival with this approach.4,4 Indeed, findings from the phase 3 DANUBE trial (NCT02516241) did not demonstrate improved OS for durvalumab in patients with PD-L1-high tumors or for durvalumab plus tremelimumab versus gemcitabine-platinum in unselected patients.5

Furthermore, the combination of PD-1/PD-L1 inhibitors with platinum-based chemotherapy in the KEYNOTE-361 and IMvigor130 trials for metastatic disease was not successful in improving survival.6,7 The combination of atezolizumab with gemcitabine-platinum in IMvigor130 (NCT02807636) demonstrated modestly improved progression-free survival (PFS; 8.2 vs 6.3 months; HR, 0.82; 95% CI 0.70-0.96; 1-sided \( P = .007 \)). Similarly, investigators in KEYNOTE-361 (NCT02853305) did not observe an improvement in OS with the combination of either atezolizumab or pembrolizumab with gemcitabine-platinum. The ongoing CheckMate-901 trial (NCT03036098) is comparing the combination of ipilimumab (Yervoy) plus nivolumab versus gemcitabine-platinum with coprimary end points of survival in cisplatin-ineligible patients and patients with PD-L1-high expressing tumors. Moreover, this trial is devoting a large substudy to examining the impact of combining nivolumab with cisplatin-gemcitabine specifically in cisplatin-eligible patients.

More recently, the landmark JAVELIN Bladder 100 phase 3 trial (NCT02603432) demonstrated that first-line switch maintenance with avelumab in patients who demonstrated a response or stable disease on 4 to 6 cycles of platinum-based chemotherapy significantly improved survival compared with best supportive care (BSC) in the overall ITT population regardless of tumor PD-L1 expression (median OS 21.4 vs 14.3 months; HR, 0.69; 95% CI, 0.56-0.86; 1-sided \( P = .0005 \)).8 Additionally, investigators reported prolonged OS in patients with PD-L1-positive tumors (HR, 0.56; 95% CI 0.40-0.79; 1-sided \( P = .0003 \)). Avelumab plus BSC also extended PFS compared with BSC alone in the ITT population (HR, 0.62; 95% CI, 0.52-0.73) as well as the PD-L1-high population (HR, 0.56; 95% CI, 0.43-0.73). These data are considered practice-changing.

Advances have occurred for the therapy of postplatinum patients with progressive metastatic disease, with FDA approvals of enfortumab vedotin-ejfv (Padcev), an antibody-drug conjugate (ADC), and the first targeted agent, erdafitinib (Balversa). In the phase 2 EV-201 trial (NCT03219333), investigators administered enfortumab vedotin, the first FDA-approved Nectin-4 targeting ADC, to 125 patients who previously received platinum-based chemotherapy and PD-1/PD-L1 inhibitors. Enfortumab vedotin induced an ORR of 44% (95% CI, 35.1%-53.2%) including 12% complete responses (CRs).9 The median PFS and OS were 5.8 and 11.7 months, respectively. Investigators observed encouraging responses even in patients with liver metastases and those with no response to prior PD1/PD-L1 inhibitor therapy. In TROPHY-U01 (NCT03547973), the ADC sacituzumab govitecan, which targets trophoblast cell-surface antigen 2, showed preliminary promise in the same setting.10 Erdafitinib, an oral FGFR inhibitor, is applicable to approximately 15% of post-platinum patients with activating genomic alterations in FGFR2 or FGFR3 and has provided advances in the salvage setting. In a phase 2 trial (N = 99) patients, ORR with erdafitinib was 40%. The median PFS was 5.5 months, and the median OS was 13.8 months.11 Ongoing phase 3 trials are attempting to validate the activity of the 2 agents.

Targeted agents for HER2-driven tumors have shown preliminary promise, which has led to early trials evaluating potent HER2 inhibitors such as fam-trastuzumab deruxtecan-nxki (Enhertu).12 PARP inhibitors and...
epigenetic modifiers have been preliminarily disappointing in unselected or selected patients.\textsuperscript{19,24}

Moreover, combinations of active agents are undergoing evaluation. The combination of enfortumab vedotin plus pembrolizumab exhibited promising activity as first-line therapy for patients with cisplatin-ineligible advanced or metastatic UC.\textsuperscript{15} The ongoing phase 3 EV-302 trial (NCT04223856) is evaluating the novel combination of enfortumab vedotin plus pembrolizumab versus gemcitabine-platinum in the first-line setting.

The combination of VEGF/FGFR inhibitors and PD-1/PD-L1 inhibitors has also shown preliminary promise. The phase 3 LEAP-011 trial (NCT03898180) is evaluating the combination of lenvatinib (Lenvima) and pembrolizumab as first-line therapy for cisplatin-ineligible mUC. The optimal sequencing of active agents needs investigation, although these efforts may have to rely on retrospective and real-world datasets.

Unfortunately, applying atezolizumab to the adjuvant setting following radical cystectomy for high-risk muscle invasive disease did not improve outcomes in the phase 3 IMvigor010 trial (NCT02450331).\textsuperscript{16} Similar efforts to evaluate pembrolizumab and nivolumab in the adjuvant setting are ongoing.

Interestingly, the phase 3 CheckMate 274 (NCT02632409) trial was reported in a news release to have met its co-primary end points of improving disease-free survival versus placebo in all randomized patients as well as in patients with tumor PD-L1 expression of 1% or higher. If these data prove practice-changing, the therapeutic landscape of first-line therapy of metastatic disease may be impacted for patients who relapse.

Neoadjuvant PD-1/ PD-L1 inhibitors alone for cisplatin-ineligible or cisplatin-refusing patients or combined with cisplatin-based chemotherapy preceding radical cystectomy have exhibited promising activity, and phase 3 trials are attempting to confirm a role for these approaches.\textsuperscript{17,18} The incorporation of PD-1/PD-L1 inhibitors in bladder-preserving trimodal chemoradiation approaches is being evaluated in ongoing phase 3 trials.

Therapy for non–muscle-invasive bladder cancer (NMIBC) has also enjoyed advances with the approval of systemic pembrolizumab for rigorously defined bacillus Calmette-Guérin (BCG)-unresponsive high-risk disease. Among 96 patients in the KEYNOTE-057 trial (NCT02625961) with high-risk BCG-unresponsive NMIBC with carcinoma in situ, the CR rate was 41% and the median duration of response was 16.2 months.\textsuperscript{19}

In April 2020, the FDA approved mitomycin gel (Jelmyto) as the first therapy indicated from the pivotal phase 3 OLYMPUS trial (NCT02793128). Forty-one of 71 patients (58%) had CR. Of those patients, 19 (46%) had durable CR at 12 months.\textsuperscript{20} Moreover, other promising intraluminally delivered agents are emerging for high-risk BCG-unresponsive NMIBC including nadofaragene firadenovc (rAd-IFN/Syn3), a non-replicating adenovirus vector harboring the human IFNA2B gene, and vicinium, a recombinant fusion protein of an anti-EpCAM antibody linked to a variant of Pseudomonas exotoxin A.\textsuperscript{21,22}

**INNOVATIONS ACROSS MODALITIES**

Blue light cystoscopy has improved the sensitivity of detection of malignancy, although further studies are ongoing to evaluate efficacy and cost effectiveness to justify universal adoption.\textsuperscript{21} Multiparametric MRI and fluorodeoxyglucose positron emission tomography imaging may warrant further evaluation to enhance clinical staging of muscle-invasive disease.\textsuperscript{24,25}

Enhanced recovery after surgery (ERAS) protocols in the setting of radical cystectomy may improve the quality of life for patients.\textsuperscript{26} Robotic cystectomy was noninferior to open cystectomy for 2-year PFS and quality of life in the phase 3 RAZOR trial (NCT01157676).\textsuperscript{27}

Finally, the emergence of intensity-modulated radiation therapy and use of MRI to plan radiotherapy may improve the therapeutic index of radiotherapy for muscle-invasive bladder cancer.

Despite these advances in therapy, it is important to not lose sight that metastatic disease is generally incurable and that clinical trials should be considered a standard of care for all settings of the disease. The critically important first step that engenders advances is the understanding of tumor biology. Novel clinical prognostic factors have been presented in the setting of PD-L1 inhibitors following platinum-based chemotherapy.\textsuperscript{28}

The Cancer Genome Atlas program has shed light on the enormous heterogeneity of tumor biology, high mutation burden, and multiple potential driver alterations in subsets of patients.\textsuperscript{29} However, we must better understand the dynamic changes in tumor and microenvironment following therapy to develop insights into resistance and new therapeutic targets. Noninvasive molecular monitoring employing cell-free DNA profiling studies of plasma and urine may provide avenues to better understand mechanisms of resistance, new therapeutic targets, and minimal residual disease.\textsuperscript{30}

Precision medicine that leverages molecular information from multiple platforms may be necessary for optimal patient selection. In this context, DNA damage repair alterations and gene expression subtypes of tumor are a step in this direction and are associated with pathologic CR to neoadjuvant cisplatin-based chemotherapy.\textsuperscript{31,32} The combination of molecular and clinical factors may also warrant exploration to develop precision medicine.\textsuperscript{33,34}
TAZVERIK is indicated for the treatment of:

- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

- **Secondary Malignancies**
  
  The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

- **Embryo-Fetal Toxicity**

  Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC(0–45h)]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

**Adverse Reactions**

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who...
THE OBJECTIVES OF THIS PROGRAM ARE TO:

- Raise awareness of TAZVERIK’s indication for patients with relapsed or refractory follicular lymphoma
- Review the mechanism of action of TAZVERIK
- Discuss TAZVERIK’s clinical trial data, including its efficacy and safety profile
- Provide information pertaining to dosing of TAZVERIK, drug interactions, use in special patient populations, and patient counseling information
- Review a hypothetical patient case

PRESENTERS

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Rocky Mountain Cancer Centers

**Sandra Kurtin, PhD, ANP-C**  
Director, Advanced Practice  
Assistant Professor, Clinical Medicine and Nursing  
The University of Arizona and Arizona Cancer Center

received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

**Drug Interactions**

Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.

Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.

Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

**Lactation**

Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

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

© 2020 Epizyme, Inc. All rights reserved. TZ-FL-BR-20-0097
TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION
Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE - TAZVERIK is indicated for the treatment of patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least 2 prior systemic therapies. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSE AND ADMINISTRATION
Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Swallow tablets whole. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia [see Adverse Reactions]</td>
<td>Neutrophil count less than 1 x 10^9/L</td>
</tr>
</tbody>
</table>
| ▶️ Withhold until neutrophil count is greater than or equal to 1 x 10^9/L, or baseline.  
 ▶️ For first occurrence, resume at same dose.  
 ▶️ For second and third occurrence, resume at reduced dose.  
 ▶️ Permanently discontinue after fourth occurrence. |

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia [see Adverse Reactions]</td>
<td>Grade 3</td>
<td></td>
</tr>
</tbody>
</table>
| ▶️ Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.  
 ▶️ For first and second occurrence, resume at reduced dose.  
 ▶️ Permanently discontinue after third occurrence. |

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 4</th>
</tr>
</thead>
</table>
| ▶️ Withhold until improvement to at least Grade 1 or baseline.  
 ▶️ For first occurrence, resume at reduced dose.  
 ▶️ Permanently discontinue after second occurrence. |

Dosage Modifications for Drug Interactions
Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 4. Dose Reduction of TAZVERIK for Moderate CYP3A Inhibitors

<table>
<thead>
<tr>
<th>Current Dosage</th>
<th>Adjusted Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg orally twice daily</td>
<td>400 mg orally twice daily</td>
</tr>
<tr>
<td>600 mg orally twice daily</td>
<td>400 mg for first dose and 200 mg for second dose</td>
</tr>
<tr>
<td>400 mg orally twice daily</td>
<td>200 mg orally twice daily</td>
</tr>
</tbody>
</table>

CONTRAINdications - None.

WARNINGS AND PREcautions
Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 668 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) occurred in 0.6% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL).

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC]0-45h) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions]; Clinical Trial Experience - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in patients with relapsed or refractory follicular lymphoma enrolled in Cohorts 4 and 5 of Study E7438-G000-101 [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily [n=99]. Among patients receiving TAZVERIK, 69% were exposed for 6 months or longer, 39% were exposed for greater than one year, and 21% were exposed for 18 months or longer. Serious adverse reactions occurred in 30% of patients receiving TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, seizures, and anemia. Eight patients (8%) permanently discontinued TAZVERIK due to an adverse reaction. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. The most frequent adverse reactions requiring dosage interruptions in ≥3% of patients were thrombocytopenia and asthenia. Dose reduction due to an adverse reaction occurred in 9 patients (9%) who received TAZVERIK. The most frequent adverse reaction requiring dose reduction in ≥3% of patients was alopecia. The most common adverse reaction (≥20%) was nausea. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 5. Laboratory Abnormalities in Patients with Relapsed or Refractory Follicular Lymphoma Receiving Tazemetostat in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Receiving Tazemetostat in Cohorts 4 and 5 of Study E7438-G000-101 (continued)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

DRUG INTERACTIONS: Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A Inhibitors: Coadministration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations [see Clinical Pharmacology], which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose as shown in Table 3 below. After discontinuation of or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce TAZVERIK dose as shown in Table 3 below.

Table 7. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Relapsed/Refractory Follicular Lymphoma Receiving Tazemetostat in Cohorts 4 and 5 of Study E7438-G000-101

- NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after 9–12 weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be lower with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human primary lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs [see Use in Specific Populations].

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

Secondary Malignancies - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see Warnings and Precautions].

Embryo-Fetal Toxicity - Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK for at least 3 months after the final dose [see Use in Specific Populations; Nonclinical Toxicology].

Lactation - Advise women not to breastfeed during treatment with TAZVERIK and for at least 3 months after the final dose [see Use in Specific Populations].
Investigators Take Stock of New Landscape for Metastatic HER2-Positive Breast Cancer

by BRITTANY LOVELY

IN THE PAST YEAR, 3 therapies have been introduced in the second and third line for patients with HER2-positive metastatic breast cancer. Although this represents a wealth of new options, experts say shaping treatment regimens for this patient population involves unpacking the nuances of clinical findings for these therapies and other available agents.

That was the goal of breast cancer specialists who participated in The Talk, an OncLive® video program, to discuss noteworthy data on efficacy and safety about fam-trastuzumab deruxtecan-nxki (Enhertu), neratinib (Nerlynx), and tucatinib (Tukysa) (TRIAL SNAPSHOTS 1-4).

Trastuzumab deruxtecan was the first of the new therapies to enter the treatment paradigm, with an FDA accelerated approval in December 2019 based on findings from the DESTINY-Breast01 trial (NCT03248492). The objective response rate in 184 patients was 60.3% (95% CI, 52.9%-67.4%), comprised of a 4.3% complete response rate and a 56.0% partial response rate. Further, the median response duration was 14.8 months (95% CI, 13.8-16.9).1

In February 2020, neratinib was approved in combination with capecitabine (Xeloda) based on data from the NALA trial (NCT01808573). The combination demonstrated median progression-free survival of 5.6 months (95% CI, 4.9-6.9) compared with 5.5 months (95% CI, 4.3-5.6) for patients treated with lapatinib (Tykerb) plus capecitabine, which translated to a hazard ratio of 0.76 (95% CI, 0.63-0.93; P = .0059). Median overall survival was 21 months and 18.7 months, respectively (HR, 0.88; 95% CI, 0.72-1.07; P = .2086).2

Although the first 2 indications were for the third-line setting and beyond, the April 2020 approval of tucatinib in combination with trastuzumab (Herceptin) plus capecitabine was specified for patients who have received 1 or more prior anti-HER2-based regimens in the metastatic setting.3 Notably, this indication also includes patients with brain metastases, a population with a great unmet need. “Nearly 50% of patients with metastatic HER2-positive breast cancer will develop brain metastases,” said Sara A. Hurvitz, MD, who served as moderator of the program. “This is an area where we need more drugs like this.”

Hurvitz was joined by Aditya Bardia, MD, MPH; Claudine J. Isaacs, MD; and Sara M. Tolaney, MD, MPH.
Tolaney, MD, MPH, to review the latest data and ongoing investigations that can further carve out a role for these agents in a complex therapeutic landscape.

**TRASTUZUMAB DERUXTECAN OFFERS PROMISE FOR HEAVILY PRETREATED PATIENTS**

**HURVITZ** For HER2-positive metastatic breast cancer, it’s been a real yawn lately, right? Only 3 FDA approvals in the past 7 months or so? It’s very exciting. We now have 7 FDA-approved drugs that target HER2 in the metastatic breast cancer setting.

Dr Bardia, if you could speak to the very exciting drug, trastuzumab deruxtecan. Can you tell us about the mechanism of action of this drug and the DESTINY Breast-01 results?

**BARDIA** Absolutely. Trastuzumab deruxtecan is a HER2-directed antibody-drug conjugate. It has several unique properties. The first is that it has a proprietary linker that allows for release of the drug potentially in the cancer cells. And also, this agent has a bystander effect, which allows the toxic payload to permeate outside of the cell membrane and affect the other cells in the microenvironment. The toxic payload with this agent is a topoisomerase 1 inhibitor, so it’s different from T-DM1 [ado-trastuzumab emtansine; Kadcyla], where the toxic payload is a [maytansine-derived toxin]. So in a number of ways, this drug is different than T-DM1 because of the bystander effect, as well as the toxic payload that it utilizes.

Investigators of DESTINY Breast-01 looked at the activity of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer who were heavily pretreated. The median number of prior lines of therapy was 6. And [I have] never seen such an impressive waterfall plot. The data showed that the agent was incredibly active, with a very high response rate and deep responses in patients who were heavily pretreated.

The data were so compelling that the FDA provided accelerated approval to this agent for patients with metastatic disease. I think it’s an excellent option to have for our patients with metastatic disease. The challenge in the clinic is the sequencing of the various agents that we have and whether one should use 1 agent over the other.

**HURVITZ** Yes, I agree. We don’t have data to guide our sequencing, and I think a lot of clinicians are using the presence or absence of brain metastases as sort of a litmus test of how to sequence tucatinib and trastuzumab deruxtecan.

**TRIAL SNAPSHOT**. Toxicity Profiles of HER2-Positive Metastatic Breast Cancer Agents

**Fam-trastuzumab deruxtecan-nxki (Enhertu)** DESTINY Breast-01 (NCT03248492) assessed trastuzumab deruxtecan monotherapy in patients with unresectable and/or metastatic HER2-positive breast cancer who received 2 or more prior anti–HER2-based regimens in the metastatic setting.

**Mechanism of action**: Trastuzumab deruxtecan is a HER2-directed antibody-drug conjugate comprised of the humanized anti-HER2 antibody IgG1 and the small molecule, DXd, a topoisomerase I inhibitor attached by a cleavable linker.

**Commonly reported adverse events in DESTINY Breast-01**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Trastuzumab deruxtecan-nxki (N = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>79%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>59%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>46%</td>
</tr>
<tr>
<td>Constipation</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Boxed warning**: interstitial lung disease and embryo-fetal harm

**Neratinib (Nerlynx)**

**NALA (NCT01808573)** assessed neratinib plus capecitabine versus lapatinib/capecitabine in patients with metastatic HER2-positive breast cancer who received 2 or more prior anti–HER2-based regimens in the metastatic setting.

**Mechanism of action**: Neratinib is an intracellular kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4.

**Commonly reported adverse events in NALA safety population**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Neratinib + capecitabine (n = 303)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>83%</td>
</tr>
<tr>
<td>Nausea</td>
<td>53%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>46%</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>45%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Tucatinib (Tukysa)**

**HER2CLIMB (NCT02614794)** evaluated tucatinib in combination with trastuzumab plus capecitabine versus placebo plus trastuzumab/capecitabine for patients with unresectable locally advanced or metastatic HER2-positive breast cancer who received 1 or more prior anti–HER2-based regimens in the metastatic setting.

**Mechanism of action**: Tucatinib is a HER2-targeted tyrosine kinase inhibitor that obstructs HER2 and HER3 phosphorylation to block downstream MAPK and AKT signaling and cell proliferation.

**Commonly reported adverse events in HER2CLIMB**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Tucatinib + trastuzumab/capecitabine (n = 404)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81%</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>63%</td>
</tr>
<tr>
<td>Nausea</td>
<td>58%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>42%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36%</td>
</tr>
</tbody>
</table>

*No grade 4 events reported.*
There are those who wonder whether we should be looking at trials to combine these 2 very active treatments. I think there are some trials that are being planned perhaps.

Dr Tolaney, can you take us through some of the important toxicities related to this therapy?

In general, from a day-to-day basis, most people tolerate the drug pretty well. They do get some GI [gastrointestinal] toxicity; patients can have some nausea, some very low-grade, mild loose stool. It actually does lower your breath for an entirely nontoxicity-related reason. So all of us need to have this on our radar, certainly, when initiating any therapy that could cause a picture that mimics COVID-19.

Dr Isaacs, could you speak about the data relating to the use of trastuzumab deruxtecan for HER2 low-expressing cancers? What are we seeing?

We have early encouraging data suggesting trastuzumab deruxtecan has activity beyond what we would think of as a traditionally HER2-positive disease. In patients with low HER2 expression, [immunohistochemistry] IHC1+ or IHC2+, the tumors are not amplified by FISH [fluorescence in situ hybridization].

There is an ongoing phase 3 trial [DESTINY Breast-04; NCT03734029] to address the activity of this drug. And as Dr Bardia mentioned, there is an interesting bystander effect and some of the questions around why it may have this activity are based on that bystander effect. I think practically speaking, it’s an incredibly important trial for us to accrue to. In the clinic today, we probably all have some patients who have these tumors that are heterogeneous, for which we’ve done biopsies at various times, with HER2-positive expression in some but HER2 low in others. These are the patients for whom I really think about using this drug with the thought that I would have activity or have the potential for activity in the different clones of the tumor.

I agree. And I think it’s a very exciting drug. I’m looking forward to seeing these data as well as the data for patients with HER2 low expression, especially triple negative, with HER1-positive and HER2-positive disease. My hope is that we’ll have some efficacy there.

Given the outstanding efficacy from this drug with a progression-free survival of 16 months in someone with a median of 6 prior lines of therapy, I think we’re really eager to figure out which patients [with pulmonary toxicity] we could reactivate the drug. I’m hoping we will learn more, but for now, those are the guidances.

I think it becomes a little trickier in the COVID-19 [coronavirus disease 2019] era, where a patient can have cough and shortness of breath for an entirely nontoxicity-related reason. So all of us need to have this on our radar, certainly, when initiating any therapy that could cause a picture that mimics COVID-19.

What was really nice about the design of HER2CLIMB was that all patients had to have received all 3 of those drugs previously. Of the results relating to outcomes for HER2CLIMB randomized trial was really focused on, I think, a really relevant patient population. For quite a while we’ve known what to do in the first-line setting and the second-line setting, but then it was sort of a free-for-all as for what to do in the third-line setting in patients who had progressed following trastuzumab- or pertuzumab-[Perjeta]-based therapy based on CLEOPATRA [NCT00567190] data or in the adjuvant or neoadjuvant setting and then after T-DM1.

What was really nice about the design of HER2CLIMB was that all patients had to have received all 3 of those drugs previously. The trial also allowed us to do something very practical, which is to allow patients with brain metastases who did not require immediate local therapy to go on a systemic therapy to see if we could control the CNS [central nervous system] disease. This was really based on trials that suggested activity for this drug and activity for some of the other TKIs in this setting, for neratinib, for instance.

Investigators also required a baseline MRI, which picked up some patients who had asymptomatic brain metastases. We know that is a problematic issue for our patients who often have HER2-positive disease and CNS involvement.

The trial design was for the treatment of patients with backbone therapy of either capecitabine/trastuzumab in a randomized placebo-controlled fashion with either tucatinib or with placebo. So the question was really, what does tucatinib add in this setting?

Results showed a statistically significant benefit in terms of progression-free survival. But perhaps most importantly,
there was also a significant survival benefit of 4.5 to 5 months or so with the addition of the tucatinib.

The percentage of patients who had brain metastases at baseline was very high, just under half the patients. And when investigators looked at the analysis, they found that the drug also had activity in that subset of patients who had brain metastases. And just to give a number on that, progression-free survival was 25% at 1 year [with tucatinib] versus 0% for patients treated with placebo.

The presentation that Nancy U. Lin, MD, gave at ASCO focused on a related but separate question. And that was really specifically looking at the control in the CNS itself, not just control everywhere. CNS progression-free survival data for the patients who had brain metastases and brain metastases that were measurable showed a significant prolongation in CNS progression-free survival as well as an overall survival benefit. Further, [benefit was also seen] for patients who had brain metastases at presentation that were new, but the investigator felt that they did not require immediate local therapy.

I think what these data show us is that we have very active agents that can help control CNS disease. These are very exciting findings.

Tucatinib’s HER2 selectivity makes it a very unique drug. Dr Tolaney, can you take us through the toxicity of tucatinib?

Tucatinib is a very potent TKI that is more focused against HER2 than some of the other TKIs. For example, neratinib is a pan-HER2 TKI, and lapatinib hits HER2 and HER1. The challenge with both lapatinib and neratinib has been the inhibition of EGFR, which has resulted in a lot of the toxicities that we’ve previously seen, such as rash or diarrhea. The advantage tucatinib has, from a toxicity profile, is that it is so selective against HER2 and really almost spares EGFR so that we are seeing much less in the way of GI toxicity.

Interestingly, tucatinib was given with capecitabine, which does cause diarrhea and PPE [palmar-plantar erythrodysesthesia]. Those rates were just slightly higher in the tucatinib arm compared with the capecitabine/trastuzumab arm. We also do see some elevation of liver function. We can see liver enzymes go up, and sometimes we see a random kind of blip in the bilirubin that can happen. It’s not common, but you can sometimes see that happen with tucatinib and then it will come down.

And so overall, I think it’s a pretty well-tolerated TKI compared with what we’re used to seeing with other TKIs.

STACKING THE DECK IN THE SECOND LINE AND BEYOND

I think it was really interesting hearing the FDA approved tucatinib in the second-line setting, so after patients had received a taxane and trastuzumab type of therapy. Are there any patients you would use this agent for in the second line?

It’s clearly an active agent, and for me, this is attractive for 2 reasons. One is that it has activity in patients with brain metastases for whom traditionally, anti-HER2 therapies have not had so much activity. And second is the excellent safety. It gives patients an option to continue with a drug that is relatively well tolerated and good for brain metastases.

One thing that was pretty interesting in the HER2CLIMB trial was that patients who developed brain metastases during the study and then received local therapy were allowed to continue on. Those patients who received tucatinib had a further delay in the development of additional brain metastases. So this would be an agent that I would be very comfortable using in the second-line setting, particularly in a patient who has a known history of brain metastases.

I would say that we’re all very focused on brain metastases because that’s a huge area of unmet need. The overall activity regardless of brain metastases was also pretty phenomenal.

On this niche topic of HER2-positive brain metastases, neratinib also had data relating to CNS outcomes from the NALA study. Neratinib has more toxicity due to the EGFR inhibition, but it is approved by the FDA in combination with capecitabine for HER2-positive metastatic breast cancer. Where do you see us using neratinib, if anywhere, in light of the very exciting tucatinib results?
CABOMETYX for severe hypertension that cannot be controlled with management; when controlled, resume at a reduced dose. Discontinue CABOMETYX in patients with uncontrolled hypertension. Monitor blood (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate hypertension, including hypertensive crisis. Hypertension occurred in 36% Hypertension and Hypertensive Crisis: CABOMETYX can cause pulmonary embolism) and arterial thromboembolism in 2% of events. Venous thromboembolism occurred in 7% (including 4% Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Grade 4 fistula or a GI perforation. DO NOT ADMINISTER CABOMETYX TO PATIENTS WHO HAVE A RECENT HISTORY OF HEMORRHAGE, INCLUDING HEMOPTYSIS, HEMATOMA, OR MELANA. HEMORRHAGE. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena. Perforations and Fistulas: Gastrointestinal GI perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation. Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention. Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

**IMPRESSIVE EFFICACY IN BOTH 1L AND 2L aRCC**

**POWERS FORWARD WITH CABOMETYX**

**THE ONLY TKI WITH SUPERIOR EFFICACY**

**FIRST- AND SECOND-LINE aRCC**

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Hemorrhage:** Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

**Perforations and Fistulas:** Gastrointestinal GI perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

**Thrombotic Events:** CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

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**Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea. Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

**Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

**Proteinuria:** Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

**Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. CABOMETYX increased the risk of ONJ. Withhold CABOMETYX for development of ONJ until complete resolution. Advise patients regarding oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices.
31466bi_RCC-5AS.indd   Custom H without notice. 1 THE ONLY TKI anti-hypertensive therapy or for hypertensive crisis. CABOMETYX for severe hypertension that cannot be controlled with management; when controlled, resume at a reduced dose. Discontinue for hypertension that is not adequately controlled with medical pressure regularly during CABOMETYX treatment. Withhold CABOMETYX in patients with uncontrolled hypertension. Monitor blood CABOMETYX can cause severe and fatal pulmonary embolism) and arterial thromboembolism in 2% of events. Venous thromboembolism occurred in 7% (including 4% fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients with a history of hemorrhage, including hemoptysis, hematemesis, or melena. CABOMETYX increased the risk of thrombotic Perforations and Fistulas: patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. Severe and fatal hemorrhages occurred with CABOMETYX. Wound complications occurred with CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or patients. Discontinue CABOMETYX for Grade 3 or 4 PPE or Grade 3 PPE. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE. Patients with moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment. Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.
5.5 Diarrhea
Diarrhea occurred in 63% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 3 diarrhea that cannot be managed with standard anti-diarrheal treatments, or Grade 4 diarrhea.

5.6 Palm-Plantar Erythrodysesthesia
Palm-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Proteinuria
Proteinuria was observed in 7% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.8 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

5.9 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematoma, or melena.

5.10 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema, can occur during treatment with CABOMETYX for up to 4 months after the last dose. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

6 ADVERSE REACTIONS
The following table represents adverse reactions that occurred with CABOMETYX that are considered to be related to treatment with CABOMETYX.

Table 1. Adverse Reactions Occurring in ≥ 10% of Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>All Grades</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74 (22)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 (15)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32 (10)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56 (17)</td>
<td>47 (15)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (1)</td>
<td>43 (10)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>11 (4)</td>
<td>10 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39 (12)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 or 4 hemorrhagic events was 3% in CABOMETYX-treated patients in RCC and HCC studies. Discontinue CABOMETYX for Grade 4 or hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematoma, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal perforations, including abscesses and sepsis, occurred in 1% of CABOMETYX-treated patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscesses and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 8% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

5.5 Diarrhea
Diarrhea occurred in 63% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 3 diarrhea that cannot be managed with standard anti-diarrheal treatments, or Grade 4 diarrhea.

5.6 Palm-Plantar Erythrodysesthesia
Palm-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Proteinuria
Proteinuria was observed in 7% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients receiving CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 50% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).
Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 1% Patients Who Received CABOMETYX in METEOR

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>CABOMETYX (n=331)</th>
<th>Everolimus (n=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>74</td>
<td>3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>68</td>
<td>3</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>53</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Increased RBC</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>25</td>
<td>1</td>
</tr>
</tbody>
</table>

Hematology

Leukopenia 35 <1 31 <1 Neutropenia 31 2 17 <1 Anemia 31 4 71 17 Lymphopenia 25 7 39 12 Thrombocytopenia 25 <1 27 <1

ALT, aspartate aminotransferase; AST, alanine aminotransferase; GGT, gamma glutamyl transferase.

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma. In which 7% of patients received CABOMETYX 60 mg once daily and 72 patients received sunitibib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitibib. Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitibib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions were: diarrhea, hypertension, fatigue, dyspnea, diastolic hypertension, asthenia, and decreased appetite which occurred in ≥ 5% of patients were: PPE, fatigue, asthenia, and decreased appetite. There were 8 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX, 53% of patients required a reduction to 20 mg daily. The most frequent adverse reactions leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased ALT. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were: PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥ 1% Patients Who Received CABOMETYX in CABOSUN

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n = 78)</th>
<th>Sunitibib (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Patients with any Grade 3-4 Adverse Reaction</td>
<td>68 65</td>
<td></td>
</tr>
</tbody>
</table>

Gastrointestinal

Diarrhea 10 11 Nausea 5 6 Vomiting 1 3 Constipation 1 0

Metabolism and Nutrition

Hypertension 9 8 Hypophosphatemia 3 7 Decreased appetite 5 1 Decreased creatinine 4 1 

Hypokalemia 3 0 Hyperparathyroidism 3 0 Hypokalemia 1 3

Skin and Subcutaneous Tissue

Palmar-planter erythrodysesthesia 8 4 Skin ulcer 3 0

Vascular

Hypertension 5 0 Hypotension 1 1 Angiopathy 1 1

Investigations

Increased ALT 5 0 Decreased ALT 4 0 Increased AST 3 3 Increased blood creatinine 3 3 Lymphopenia 1 6 Thrombocytopenia 2 1

Nervous System

Syncope 5 0

Respiratory, Thoracic, and Mediastinal

Dyspnea 1 6 Dysphonia 1 0

Blood and Lymphatic

Anemia 1 3

Psychiatric

Depression 4 0 Confusional state 1 1

Infections

Lung infection 4 0

Musculoskeletal and Connective Tissue

Back pain 5 1 Bone pain 3 1 Pain in extremity 3 0 Arthritis 1 0

Renal and Urinary

Renal failure acute 4 1 Proteinuria 3 1

Hepatobiliary Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were: PPE, hypertension, fatigue, diastolic hypertension, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX, 53% of patients required a reduction to 20 mg daily. The most frequent adverse reactions leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased ALT. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were (PPE) 2%, fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 4. Adverse Reactions Occurring in ≥ 5% of CABOMETYX-Treated Patients in CELESTIAL

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n = 467)</th>
<th>Placebo (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Patients with any Grade 3-4 Adverse Reaction</td>
<td>48 48</td>
<td></td>
</tr>
</tbody>
</table>

Gastrointestinal

Diarrhea 54 49 Nausea 31 28 Vomiting 26 <1 12 3 Stomatitis 13 <1 2 0 Osteoporosis 19 <1 3 0

Dyspnea 10 <1 3 0

General

Fatigue 45 10 30 4 Anemia 22 7 8 2

Mucosal Inflammation 14 2 2 <1

Metabolism and Nutrition

Decreased appetite 48 6 18 <1

Skin and Subcutaneous Tissue

Hyperpigmentation 46 17 9 0 Rash 21 2 9 <1

Vascular

Hypertension 30 16 6 2

Investigations

Weight decreased 17 1 6 0

Nervous System

Dyspnea 12 0 2 0

Endocrine

Hypothyroidism 8 <1 <1 0

Respiratory, Thoracic, and Mediastinal

Dyspnea 19 1 2 0

Dyspnea 12 3 10 <1

Musculoskeletal and Connective Tissue

Pain in extremity 9 <1 4 1

Muscle spasms 8 <1 2 0

includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4).

1 Includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4).

2 NCI CTCAE Version 4.0

3 Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash macular-papular, rash papular, rash pruritic, rash purpuric, rash vesicular, dermatitis acneform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected.

4 Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased.
malformations and variations including reduced spleen through organogenesis resulted in findings of visceral [AUC] at the recommended dose). Findings included organogenesis caused increased embryo-fetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hyperactivity was observed at both doses tested on Postnatal Day 22. Targeted were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner’s gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physisphy hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 46% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdose was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive impairment, and Grade 3 hypokalemia. The patient may have also had Grade 2 mental status changes. It is unknown how cabozantinib is handled in overdose situations.

11 PATIENT COUNSELING INFORMATION

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.
TILs, the Ultimate in Personalized Immunotherapy, Move Closer to Market

by JANE DE LARTIGUE, PhD

UNTIL NOW, THE FIELD OF cell-based immunotherapy has been dominated by chimeric antigen receptor (CAR) T cells, with groundbreaking FDA approvals for 3 drugs across several types of hematologic malignancies. In solid tumors, however, CAR T-cell therapies have yet to gain ground.1,2 Headline-making data have shined a light on a closely related form of cell-based immunotherapy: tumor-infiltrating lymphocytes (TILs).3-5 Despite having demonstrated promising activity in patients with metastatic melanoma, TIL products have had limited marketability due to a time-consuming and costly manufacturing process.6-8 Yet, the enduring appeal of TILs lies in the fact that they already are trained to recognize a patient’s specific tumor antigens and, unlike CAR T cells, do not need to be genetically engineered.6-8 The persistence of academic institutions and pharmaceutical companies over the past 4 decades in pursuing these therapies may be about to pay off.

Capitalizing on a streamlined manufacturing process, Iovance Biotherapeutics has developed several new TIL products.9 Lifileucel (LN-144) has produced substantial clinical responses in patients with metastatic melanoma previously treated with systemic therapy, including an immune checkpoint inhibitor (ICI).3,10 Meanwhile, data from clinical trials with another Iovance TIL product, LN-145, and a TIL therapy developed at Moffitt Cancer Center in Tampa, Florida, provide examples of the mounting evidence of the activity of TIL therapy in other types of solid tumors.4,5 With Iovance reporting plans to file for regulatory approval for lifileucel in metastatic melanoma and for LN-145 in cervical cancer in the near future,10,11 the first FDA-approved TIL-based therapies may finally reach the clinic.

EXPLOITING T CELLS

TIL therapies, a form of adoptive cell transfer, capitalize on the underlying genomic instability of cancer cells, which causes the accumulation of genetic mutations that give rise to antigens for which expression is limited to tumors (neoantigens). Upon recognition of these neoantigens, cytotoxic T lymphocytes (CTLs) become activated, provoking an antitumor immune response. Tumor-specific CTLs have been found in the blood and tumor tissue of patients with cancer. The latter, referred to as TILs, can engage in tumor cell killing upon recognition of their cognate ligand.12,13

There is significant heterogeneity across cancer types with regard to the density of TILs, with tumors broadly categorized as immunologically “hot” or “cold” based in part on this metric.14,15 Although a high degree of lymphocytic infiltration is associated with good prognosis in several cancer types, tumors have evolved...
numerous mechanisms to suppress the immune response.\(^{12}\)

The goal of immunotherapy is to amplify or reestablish a patient’s antitumor immune response. Because of their central role in tumor cell killing, T cells have been the focus of immunotherapeutic design, leading to groundbreaking developments in the form of small-molecule ICIs and cell-based immunotherapies.

The most renowned example of the latter is CAR T-cell therapy: T cells collected from the peripheral blood are genetically modified to recognize a tumor antigen and direct their cytotoxic activity against the cancer cells expressing it. Despite substantial success culminating in FDA approvals across several types of hematologic malignancies, CAR T cells face a number of challenges.\(^{1,2}\)

An alternative to CAR T-cell therapy is TILs, which are harvested from the tumor. As a polyclonal pool that has already encountered the patient’s cancer cells, TILs are enriched for T cells endowed with natural reactivity against a variety of tumor antigens. Because TILs come directly from a patient’s own tumor, they represent the ultimate form of personalized therapy.\(^{6-8}\)

**TIL THERAPY**

TIL therapy was pioneered at the National Cancer Institute (NCI) beginning in the late 1980s, notably by Steven A. Rosenberg, MD, PhD, a 2013 Giants of Cancer Care award winner.\(^{10}\) In a series of seminal studies, lymphocytes were extracted from tumor tissue that had been resected from patients with metastatic melanoma. After being rapidly expanded outside the body and then reinfused into the same patient, these lymphocytes could induce tumor regression.\(^{17-19}\)

Across these and other studies conducted at academic institutions around the world, TIL therapy has consistently achieved objective response rates (ORRs) of 40% to 50% in patients with melanoma, including complete responses (CRs) in 10% to 20% of patients. These CRs were often durable, lasting 3 to 5 years.\(^{8}\)

Despite these impressive results, TIL therapy has not been commercialized, largely because of the significant cost and complexity of the manufacturing process and the overshadowing of TILs by the development of ICIs for metastatic melanoma treatment.\(^{6-8}\)

The TIL manufacturing process begins with the resection of 1 or more tumor lesions, dissection of the resected tissue into multiple smaller fragments, and culture of those fragments in a growth medium enriched with interleukin 2 (IL-2), which facilitates outgrowth of the TILs from the tumor tissue (figure).\(^{6-8}\)

In the original protocol, several TIL cultures are established per patient and tested for recognition of the patient’s tumor cells using an assay that measures the production of effector cytokines, such as interferon gamma. Reactive cells are pooled and then undergo a rapid expansion phase, in which they are cultured with IL-2, an anti-CD3 antibody, and irradiated peripheral blood mononuclear “feeder” cells, all of which support the activation and propagation of the TILs. The total time from tumor resection to final TIL product is between 5 and 7 weeks with this protocol.\(^{6-8}\)

Before TILs can be reinfused, patients undergo a lymphodepleting conditioning regimen to optimize the environment into which the TILs are introduced, predominantly by depleting immunosuppressive cells. This is achieved through chemotherapy with cyclophosphamide and fludarabine and/or total body irradiation.\(^{6-8}\)

Because they recognize antigens specific to the individual patient’s tumor, TILs cause off-target toxicity more rarely than CAR T cells. The most common toxicities are related to the lymphodepleting regimen; thus, efforts to further optimize it are ongoing.\(^{6-8}\)

**ADVANCING TIL THERAPY**

The prospect of truly personalized therapy with durable efficacy and limited toxicity has lent an enduring appeal to TIL therapy and several types of approaches are under study (table). Continued efforts to advance its clinical development have mainly focused on reducing production time.

Investigators at the NCI developed a “young TIL” process, which shortens the production process by eliminating the original protocol’s cytokine measurement step to select tumor-reactive TILs.\(^{6,20}\)

Among the most successful efforts to streamline TIL production is Iovance Biotherapeutic’s Gen 2 process, which takes just 22 days. Iovance has reported that TIL manufacture has been successful for over 90% of more than 300 patients. The company has also developed a Gen 3 process, further decreasing the manufacturing time to 16 days. Both processes are being used in ongoing clinical development of Iovance’s TIL products lifileucel and LN-145.\(^{7,9}\)

The C-144-01 trial (NCT02360579) is a multicohort phase 2 clinical trial of lifileucel in patients with metastatic melanoma who have received at least 1 prior systemic therapy, including an ICI.

Long-term data from cohort 2, presented at the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program, demonstrated an ORR of 36.4% and 2 CRs among 66 patients at a median follow-up of 18.7 months.\(^3\)

All patients experienced at least 1 treatment-emergent adverse event (TEAE), most commonly thrombocytopenia, chills, anemia, pyrexia, neutropenia, and febrile neutropenia, and 97% experienced grade 3/4 TEAEs, predominantly thrombocytopenia, anemia, and febrile neutropenia.

An additional 75 patients were enrolled in cohort 4 of this study, designed to serve as the pivotal cohort in support of a biologics license application that Iovance hopes to file soon. Initial results revealed an ORR of 32.4%, including 1 CR, in 68 evaluable patients after a median follow-up of 5.3 months.\(^{10}\)
BEYOND MELANOMA

TIL research and development has focused on melanoma, but investigators have recently had success growing TILs from multiple other tumor types. There have been case reports of durable remissions in patients with metastatic colorectal cancer, cholangiocarcinoma, and breast cancer.\(^6,21\)

Several reports have demonstrated the feasibility of isolating TILs from metastatic non–small cell lung cancer (NSCLC), in addition to showing encouraging preliminary signs of clinical activity.\(^21\) In recently presented results of a phase 1 clinical trial (NCT03215810), patients with metastatic NSCLC who had progressed on nivolumab (Opdivo) received a TIL product manufactured at Moffitt Cancer Center.

Patients received nivolumab 240 mg every 2 weeks for 4 cycles. Those who showed signs of progression were then treated with TILs, followed by nivolumab 480 mg every 4 weeks for up to a year. At the time of the presentation, 20 patients had been enrolled, of whom 13 had progressed on nivolumab and received TILs and 2 were scheduled to receive TILs. Two patients had achieved durable CRs, which were ongoing at almost 1 year.

An additional 3 patients achieved clinical remission, which they maintained with local ablative therapy performed between 6 months and 17 months post TIL infusion, after isolated new lesions emerged. The majority of AEs resolved quickly, with common nonhematologic AEs including hyperbilirubinemia, hypophosphatemia, nausea, hyponatremia, and diarrhea.\(^6,22\)

Meanwhile, LN-145 is being evaluated in the ongoing phase 2 C-145-04 trial (NCT03108495) in patients with metastatic or persistent cervical cancer. Preliminary results were presented at the 2019 ASCO Annual Meeting.

Among 27 patients, the ORR was 44.4%, with 3 CRs. Median duration of response was not reached at a median follow-up of 7.4 months. The most common TEAEs were chills, anemia, diarrhea, pyrexia, and thrombocytopenia. Overall, 96.3% of patients experienced grade 3/4 TEAEs, most commonly anemia and thrombocytopenia.\(^5\)

On the basis of these data, LN-145 was awarded breakthrough therapy and fast track designations by the FDA, and Iovance plans to use the C-145-04 trial results to support an application for approval in patients with cervical cancer.\(^11,23,24\)

CHALLENGES REMAIN

Despite significant promise, challenges to...
broad clinical implementation of TIL therapy remain. Many tumor types are not very immunogenic, with TILs limited in number or subject to immunosuppressive factors in the tumor microenvironment that restrict their cytotoxic activity.\textsuperscript{13,25}

Investigators are exploring ways to further enhance the survival, expansion, and cytotoxic activity of TILs through, for example, addition of costimulatory antibodies to the culture medium (NCT02652455, NCT03610490).\textsuperscript{8,26,27} They are also evaluating new means of selecting the tumor-reactive populations of cells from among TILs.\textsuperscript{8}

Iovance is developing LN-145-S1, a TIL product expanded from the subset of PD-1–expressing cells in the tumor infiltrate, which may select for tumor-reactive CD8+ T cells.\textsuperscript{9,28} Similarly, a human papillomavirus (HPV)–selected TIL product was recently developed, which produced an ORR of 28% among 18 patients with HPV-associated cervical cancer (NCT01585428). Two patients had ongoing CRs, which lasted more than 4 years.\textsuperscript{29}

Achilles Therapeutics is developing ATL001, a TIL product that is selectively enriched for T cells targeting clonal neoantigens, which arise from the earliest stages of cancer development and should be present in all cancer cells.\textsuperscript{21}

The company’s manufacturing process involves analyzing blood and tumor samples via whole-exome and -transcriptome sequencing to identify candidate clonal neoantigens. Dendritic cells (DCs) isolated from the patient’s blood are then loaded with peptides corresponding to these antigens and are cultured with TILs to activate and expand T cells that recognize the specific antigens expressed by the DCs. Phase 1/2 clinical trials of ATL001 are under way.\textsuperscript{21}

In efforts to overcome the immunosuppressive tumor microenvironment, TILs have been genetically modified to express a dominant-negative form of the TGF-β receptor, which helps the TILs resist the T-cell–inhibitory effects of TGF-β. This TIL product is currently being evaluated in clinical trials (NCT01955460, NCT02650986). Additionally, investigators have transduced TILs with genes encoding chemokine receptors to promote homing of the cells to the tumor site.\textsuperscript{30,31}

Finally, investigators are examining the possibility of extracting tumor-reactive T cells from bone marrow, dubbed marrow-infiltrating lymphocytes (MILs), to treat hematologic malignancies. These cells have exhibited highly tumor-specific properties when activated and expanded in samples from patients with multiple myeloma.\textsuperscript{32}

WindMIL Therapeutics is developing both unmodified MILs and gene-modified CAR-MILs. The company initiated a phase 2 study (NCT04069936) of MILs in patients with metastatic NSCLC in late 2019, the design of which was highlighted at ASCO 2020.\textsuperscript{33,34} WindMIL Therapeutics also recently presented preclinical data demonstrating superior antitumor efficacy of CAR-MILs compared with conventional CAR T-cell therapy in cultured cells and a mouse model of multiple myeloma.\textsuperscript{35}
The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

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

To nominate, please visit: giantsofcancercare.com/nominate

**PROGRAM OVERVIEW**

- Nominations are open through 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.
4 Biomarker-Driven Regimens Propel Frontline Advances in Ovarian Cancer

by CHRISTINA T. LOGUIDICE

TARGETED THERAPY APPROACHES have expanded rapidly in ovarian cancer over the past 3 years, with the FDA approving 4 new strategies in frontline settings that allow women to remain free of disease progression longer than the previous standard of care. These developments are generating excitement in a field where, despite improvements in surgical techniques and chemotherapy regimens, most patients with advanced disease relapse within the first 2 years.¹

During an OncLive Peer Exchange, a panel of ovarian experts discussed the clinical trials that led the FDA to broaden approvals for bevacizumab (Avastin), olaparib (Lynparza), niraparib (Zejula), and the combination of olaparib and bevacizumab in first-line and maintenance settings (TIMELINE).² They also examined the emergence of homologous recombination deficiency (HRD) as a new biomarker to help guide decision-making.

The pace of change in frontline advanced ovarian cancer has been “pretty impressive,” said Bradley J. Monk, MD, who served as moderator for the program. “Before that, it was almost 20 years since the standard had changed away from cyclophosphamide to paclitaxel,” he said. “It’s a very exciting time.”

GOG-0218: BEVACIZUMAB
Based on data from the phase 3 GOG-0218 trial (NCT00262847), the FDA approved bevacizumab in June 2018 for patients with epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, for stage III or IV disease after initial surgical resection.³

Panelist Michael J. Birrer, MD, PhD called it “the granddaddy of the trials” because findings from the study, launched in 2005, led to the introduction of the first biologic agent and targeted therapy for ovarian cancer into clinical practice. Bevacizumab first gained FDA approval in combination with chemotherapy in the recurrent, platinum-resistant setting in 2014.⁴

In GOG-0218, investigators randomly assigned 1873 women with incompletely resectable, newly diagnosed stage III or IV disease to standard carboplatin plus paclitaxel chemotherapy followed by placebo maintenance, standard chemotherapy plus concurrent bevacizumab followed by placebo maintenance, or standard chemotherapy plus concurrent and maintenance bevacizumab.

After a median follow-up of 17.4 months, the median progression-free survival (PFS) was 10.3 months in the control group, 11.2 months in the bevacizumab-initiation group, and 14.1 months in the bevacizumab-throughout group. Relative to controls, HR for progression or death was 0.908 (95% CI, 0.795-1.040; P = .16) in the bevacizumab-initiation arm and 0.717 (95% CI, 0.625-0.824; P < .001) in the bevacizumab-throughout arm. There were no
significant differences in overall survival (OS) between groups.\(^5\)

A long-term follow-up of the study for a median of 102.9 months confirmed these findings. Compared with the control arm, HR for death was 1.06 (95% CI, 0.94-1.20) in the bevacizumab-initiation arm and 0.96 (95% CI, 0.85-1.09) in the bevacizumab-throughout arm.\(^6\)

Although that lack of an OS benefit persisted, Birrer said, "a subset analysis looking at some high-risk patients, like stage IV, suggested that they may have benefited the most and had a survival advantage." The median OS for patients with stage IV disease assigned to bevacizumab-throughout was 42.8 months versus 32.6 months for similar patients in the control arm (HR, 0.75; 95% CI, 0.59-0.95).

The panelists said the European Medicines Agency approved bevacizumab for the treatment of ovarian cancer in 2011. They noted that it took longer for US approval because OS was considered a key end point by the FDA at that time.

"Back then, we were looking to hit the OS mark," Leslie Randall, MD, said. "In that interim time, that’s when we had talks with the FDA that OS was not the best end point in ovarian cancer and that the earlier the line of therapy, the more difficult it is as an end point."

Monk further explained that other factors now weigh more heavily into ovarian cancer approval decisions, including a meaningful PFS benefit, good safety/tolerability, and convenience. Bevacizumab fulfills those other concerns, making the anti-VEGF monoclonal antibody a valuable treatment option in this setting.

**SOLO-1: OLAPARIB**

In December 2018, the FDA approved the PARP inhibitor olaparib as a maintenance treatment for adults with deleterious or suspected BRCA-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to first-line platinum-based chemotherapy based on data from the phase 3 SOLO-1 trial (NCT01844986).\(^7\) "The BRCA mutation could be either germline or somatic, although as we all know, the majority of these patients did have a germline mutation," said Shannon N. Westin, MD, MPH, noting that only 2 patients in the trial had a somatic mutation.

In SOLO-1, patients were randomly assigned to maintenance therapy with 300 mg twice-daily olaparib (n = 260) or placebo (n = 131).\(^8\) Olaparib was associated with a 70% reduction in the risk for progression or death (HR, 0.30; 95% CI, 0.23-0.41; \(P < .001\)) at a median follow-up of 41 months. "We were excited about the hazard ratio of 0.7 [in the GOG-0218 trial], but now...\(\)
here we were with a 0.3—a 70% reduction in the risk of progression,” Westin said. She added that investigators followed patients in the study and observed some remarkable results. “A year after the majority of those patients had stopped treatment, 60% of the patients on the olaparib arm were progression free compared with 26.9% who were progression free at 3 years who were on placebo,” she said.

Westin explained that these data helped demonstrate that targeted maintenance works in ovarian cancer and that patients can safely stop maintenance therapy. That said, it is still unclear whether olaparib treatment will yield an OS benefit. “That’s the next big question,” she said. “It’s going to take a while to get that answer, but certainly impressive data that led to an FDA approval for this drug.”

Monk asked the panelists what they thought about the risks of myelodysplastic syndrome (MDS), which has been observed in less than 1.5% of patients who received olaparib monotherapy in clinical trials. Many of those MDS events were fatal.9

“Predictively, that 1% range is certainly something to consider, but when you see such a difference in PFS, we can feel quite confident that olaparib is improving the quality of patients’ lives, and they’re likely living longer,” said panelist Matthew Powell, MD. He added that the olaparib data reflect the benefit of biomarker-directed therapy and that they have driven what he would consider the standard of care for these patients.

Five-year follow-up data presented at the European Society for Medical Oncology Virtual Congress 2020 in October showed that the benefit of olaparib continues substantially beyond the end of treatment. The median PFS observed with olaparib maintenance was 56.0 months compared with 13.8 months in the placebo arm (HR, 0.33; 95% CI, 0.25-0.43).10

PRIMA: NIRAPARIB
In April 2020, the FDA approved niraparib as a maintenance therapy for adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to first-line platinum-based chemotherapy based on data from the phase 3 PRIMA trial (NCT02655016). Unlike SOLO-1, all biomarker populations were included in the study and 50.9% of patients had HRD-positive tumors.11

“This was an interesting trial in that it had entered the worst [prognosis] patients—stage III/IV, high-grade serous or endometrioid who had stage III, primary debulked with visible or residual disease, either neoadjuvant or inoperable—really high-risk disease and all stage IV,” Randall said. “I thought this trial would be negative because of the high-risk population, but it was not. It did show a benefit.”

Patients were assigned to maintenance therapy with niraparib (n = 487) or placebo (n = 246). In the overall study population, the PFS was 13.8 months for niraparib and 8.2 months for placebo (HR, 0.62; 95% CI, 0.50-0.76; P < .001). Among the patients with HRD, the median PFS was 21.9 months in the niraparib group versus 10.4 months in the placebo group (HR 0.43; 95% CI, 0.31-0.59; P < .001).12

“If you then looked at the BRCA wild-type HRD, there was a 0.50 HR,” Randall said, noting she was surprised by these data because she did not expect to see this degree of benefit in the higher-risk population. “If you looked from the first patient enrolled in PRIMA to the FDA approval on April 29, it was 37 months,” Monk added. “We changed the standard of care in ovarian cancer in all comers in 37 months, whereas GOG-0218 took more than 10 years from the time that the study started until it got FDA approval. That’s important.”

Monk also pointed out that PRIMA redefined how ovarian cancer studies are conducted. “What PRIMA did was very collaborative, not only with the GOG [Foundation] beyond the government, but with our European colleagues [as well],” he said. “That’s the new standard moving forward as these are now international trials with the European Network of Gynaecological Oncological Trial Groups and the GOG.”

PAOLA-1: OLAPARIB PLUS BEVACIZUMAB
In May 2020, the FDA expanded the indication for olaparib to include its combination with bevacizumab for first-line maintenance treatment of adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to first-line platinum-based chemotherapy and with HRD-positive status defined by either a deleterious or suspected deleterious BRCA mutation and/or genomic instability. Approval was based on the phase 3 PAOLA-1 trial (NCT02477644), in which patients were randomly assigned 2:1 to receive bevacizumab in combination with olaparib at 300 mg twice daily (n = 537) or with placebo (n = 269). Patients continued olaparib for up to 2 years or until disease progression or unacceptable toxicity.13

“It had impressive results,” Powell said of the trial. “It was an amazing difference that we’re seeing, and we’re quite excited.”

After a median follow-up of 22.9 months, the median PFS was 22.1 months in the combination arm compared with 16.6 months with placebo plus bevacizumab (HR, 0.59; 95% CI, 0.49-0.72; P < .001).

Among patients with HRD-positive tumors, the median PFS was 37.2 months in the olaparib arm versus 17.7 months in the placebo arm in those with concomitant BRCA mutations (HR, 0.33; 95% CI, 0.25-0.45) and 28.1 months versus 16.6 months, respectively, in those without BRCA mutations (HR, 0.43; 95% CI, 0.28-0.66).14

“We used to follow our patients every 3 months for 2 years because they almost all recur by 2 years. That doesn’t work anymore. Now you need to follow your patients very carefully for a long time because the recurrences have been prolonged: 3 years at the median," Monk said.

The bevacizumab/olaparib regimen did not raise any significant safety concerns beyond...
what was expected. “We’re well versed in the use of bevacizumab, and there was no unique toxicity signal seen with that combination,” Powell said. “It is easy to do, and patients tolerate it well. There were at least additive effects for the 2 targeted therapies and maybe even a little more; it’s hard to tell for sure.”

MAKING SENSE OF HRD STATUS

HRD status has recently emerged as a biomarker for ovarian and other cancers. Investigators in the PRIMA and PAOLA-1 trials included HRD status as a marker, but it is still poorly understood. Randall explained that HRD is a phenotypic assay of DNA repair deficiency consisting of 3 components: loss of heterozygosity, telomeric allelic imbalance, and a large-scale state transition.

“There is a score of which somatic BRCA is a part. The scoring is complicated, but the cutoff is generally set at 42,” Randall said. That was the cutoff in PRIMA and PAOLA-1, but there is flexibility since that cutoff has not yet been stringently validated, she added.

Randall acknowledged that HRD is not a perfect biomarker but said HRD status is a helpful measure in the up-front setting.

Monk added, “When I look at PRIMA versus PAOLA-1, 2 very impactful frontline trials, I see there was an impact in the HRP [homologous recombination proficient] group, in other words, the non-HRD group. I didn’t see that in PAOLA-1.”

The panelists surmised that there may be many reasons for the discrepancy between the results.

“The PAOLA-1 patient population is quite different than the population from PRIMA, which had more bad actors. Perhaps you’re seeing a difference that may be statistically significant, but how clinically significant is it, based on the patient population?” Westin asked, noting that the patients in the PAOLA-1 study were getting bevacizumab, a known active drug, and not placebo, which could have had an impact.

Powell said there is no way to know the true effects of these agents in the HRP population and whether one agent is superior to the other without a head-to-head comparison of niraparib and olaparib. “It’s nice that we have an option for PARP inhibition in our proficient patients,” he said. “I’ll leave it at that and say, ‘Thank you, FDA, for giving us some choices.’”

REFERENCES
7. FDA approved olaparib (Lynparza). AstraZeneca Pharmaceuticals LP for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based. FDA. Updated December 26, 2018. Accessed October 25, 2020. https://bit.ly/3ICoACj

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Mixed Record for Immunotherapy
Ursula Matulonis, MD, delves into recent clinical findings for PD-1/PD-L1 inhibitors in patients with gynecologic cancers. Clinical activity has been moderate, with a failure to elicit significant responses in newly diagnosed and adjuvant treatment settings, Matulonis said. A greater understanding of molecular subtypes might yield candidates for pan-tumor therapeutic approaches.

Matulonis is chief of the Division of Gynecologic Oncology and Brock-Wilson Family Chair at the Dana-Farber Cancer Institute, and professor of Medicine at Harvard Medical School in Boston, Massachusetts.

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Overcoming PARP Resistance
New strategies are needed to overcome resistance in patients with ovarian cancer who are treated with PARP inhibitors, says Gottfried E. Konecny, MD. These may include trying to recover homologous recombination proficiency and combining PARP inhibitors with immunotherapy. “The bottom line is that there are more possible drug combinations,” said Konecny, an associate professor of medicine and lead clinician for gynecologic oncology in the Department of Medicine at the University of California, Los Angeles.

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Making Choices in Recurrent Settings
Amanda L. Jackson, MD, discusses clinical considerations involved in choosing between a VEGF inhibitor and a PARP inhibitor in patients with recurrent, platinum-sensitive ovarian cancer.

Factors to consider include earlier lines of therapy, the presence of a BRCA mutation, and what adverse effects the patients is experiencing.

Jackson is an associate professor of Obstetrics & Gynecology and division director of the University of Cincinnati Health in Ohio.

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