Traina Helps Navigate Surge of New Breast Cancer Therapies

PEER EXCHANGE
More Options for HER2+ MBC

TIGIT Checkpoint Attracts Interest

COVID-19 IN THE CLINIC
Mortality May Be Higher in Patients With Cancer

CONFERENCE HIGHLIGHTS
21st Annual International LUNG CANCER Congress

CLINICAL PERSPECTIVES
GU TUMORS
Brian I. Rini, MD, Reviews Key ASCO Abstracts

THE TALK
Experts Tackle GI CANCERS

DRUG SPOTLIGHT
HEMATOLOGIC MALIGNANCIES
Kami J. Maddocks, MD, Discusses New DLBCL Option

VANDERBILT-INGRAM CANCER CENTER
Palliative Care for Young Adults Is a Growing Reality in CRC
BY RAJIV AGARWAL, MD, AND CATHY ENG, 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.

Please see additional Important Safety Information on the adjacent page.
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.

Important Safety Information (continued)

especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

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

The most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA 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%).


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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NPYR20000017 August 2020
Produced in USA.

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

ZELURA (niraparib) capsules, for oral use

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

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer

ZELURA 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.

1.2 Maintenance Treatment of Recurrent Ovarian Cancer

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

1.3 Treatment of Advanced Ovarian Cancer after Three or More Chemotherapies

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

- a deleterious or suspected deleterious BRCA mutation, or
- genomic instability and who have progressed more than six 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 test for ZELURA.

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 ZELURA monotherapy in clinical trials. In 1765 patients treated with ZELURA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZELURA 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 radiotherapy. Discontinue ZELURA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression

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

In PRIMA, the overall incidence of Grade 3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZELURA. 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 ZELURA based on baseline weight or platelet count, Grade 3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZELURA. 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 ZELURA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients. In QUADRA, Grade 3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 28%, 27%, and 13% of patients receiving ZELURA. 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 patients who received ZELURA in the pooled PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (65%), anemia (65%), fatigue (55%), constipation (55%), mucositis (53%), abdominal pain (53%), vomiting (33%), neutropenia (33%), decreased appetite (24%), leukopenia (24%), insomina (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dyspnea (14%), acute kidney injury (13%), urinary tract infection (10%), and hyponatremia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer

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

Table 1: Adverse Drug Reactions Reported in ≥5% of All Patients Receiving ZELURA in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA</td>
<td>Placebo</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
</tr>
</tbody>
</table>

Table 1: Adverse Drug Reactions Reported in ≥5% of All Patients Receiving ZELURA in PRIMA

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<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
</tr>
</tbody>
</table>

All Patients Receiving ZELURA in PRIMA

Serious adverse reactions occurred in 12% of patients receiving ZELURA. Serious adverse reactions in ≥2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (one patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZELURA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZELURA included thrombocytopenia (3.7%), 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 ZELURA in the PRIMA study.

*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.

**CICAE:Common Terminology Criteria for Adverse Events version 4.02 includes neutropenia, neutropenic infection, neutropenia spongob, 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 ZELUSA in PRIMA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=169</td>
<td>N=244</td>
</tr>
</tbody>
</table>

- Decreased hemoglobin: 87/66 (29/1)
- Decreased platelets: 74/13 (37/0)
- Decreased leukocytes: 71/36 (9/0)
- Increased glucose: 66/57 (3/3)
- Decreased neutrophils: 66/25 (23/1)
- Decreased lymphocytes: 51/29 (7/3)
- Increased alkaline phosphatase: 46/21 (1/0)
- Increased creatinine: 40/23 (0/0)
- Increased magnesium: 36/34 (1/0)
- Increased aspartate aminotransferase: 35/17 (1/0.4)
- Increased alanine aminotransferase: 29/17 (2/1)

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=169</td>
<td>N=244</td>
</tr>
</tbody>
</table>

- Decreased hemoglobin: 81/70 (21/0)
- Decreased leukocytes: 70/46 (6/0)
- Decreased platelets: 63/15 (18/0)
- Increased glucose: 63/36 (2/1)
- Decreased neutrophils: 60/27 (15/0)
- Decreased lymphocytes: 52/30 (5/4)
- Increased alkaline phosphatase: 43/17 (1/0)
- Increased creatinine: 41/22 (0/0)
- Increased aspartate aminotransferase: 31/19 (1/0)
- Increased alanine aminotransferase: 28/15 (2/2)

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

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=169</td>
<td>N=244</td>
</tr>
</tbody>
</table>

- Decreased hemoglobin: 81/70 (21/0)
- Decreased neutrophils: 60/27 (15/0)
- Increased alkaline phosphatase: 43/17 (1/0)
- Increased creatinine: 41/22 (0/0)
- Increased alanine aminotransferase: 28/15 (2/2)

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELUSA monotherapy 300 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 ZELUSA in these patients was 250 days.

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZELUSA in NOVA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=567</td>
<td>N=179</td>
</tr>
</tbody>
</table>

- Decrease in hemoglobin: 85/56 (25/0.5)
- Decrease in platelet count: 72/21 (35/0.5)
- Decrease in total white blood cells (WBC): 66/37 (7/0.7)
- Decrease in absolute neutrophil count: 58/25 (21/7)
- Increase in AST: 36/23 (1/0)
- Increase in ALT: 28/15 (1/2)

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELUSA in NOVA

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELUSA</td>
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</tr>
<tr>
<td>N=567</td>
<td>N=179</td>
</tr>
</tbody>
</table>

- Decrease in hemoglobin: 85/56 (25/0.5)
- Decrease in platelet count: 72/21 (35/0.5)
- Decrease in total white blood cells (WBC): 66/37 (7/0.7)
- Decrease in absolute neutrophil count: 58/25 (21/7)
- Increase in AST: 36/23 (1/0)
- Increase in ALT: 28/15 (1/2)

Note: Decrease in hemoglobin: 85/56 (25/0.5)
alkaline phosphatase increased, weight decreased, depression, gastritis.

Treatment of Advanced Ovarian Cancer After Three or More Chemotherapies

The safety of ZEJULA monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 448 patients with recurrent high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range 0.03 to 32 months). For the indicated QUADRA population, the median duration was 4 months (range 0.1 to 30 months).

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

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

Permanently discontinuation due to adverse reactions (Grade 4) occurred in 21% of patients who received ZEJULA.

Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), nausea (22%), neutropenia (11%), anemia (11%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

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

| Table 7: Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                                   | Grades 1–4 | Grades 3–4 |
|                                   | N=1663 | N=1663 | N=1663 | N=1663 |
| Blood and Lymphatic System Disorders |
| Anemia a                                      | 51.7 | 21.0 |
| Neutropenia b                                 | 52.1 | 28.1 |
| Gastrointestinal Disorders                  |
| Nausea                                        | 67.7 | 10.0 |
| Vomiting                                      | 44.8 | 8.0 |
| Constipation                                  | 36.5 | 5.0 |
| Abdominal pain                                | 34.7 | 7.0 |
| Diarrhea                                      | 17.2 | 0.2 |
| General Disorders and Administration Site Conditions |
| Fatigue                                       | 56.7 | 7.0 |
| Infections and Infestations                  |
| Urticarial reaction                           | 15.2 | 2.0 |
| Investigations                                |
| Blood alkaline phosphatase increased          | 11.2 | 1.1 |
| AST/ALT elevation                             | 11.1 | 1.1 |
| Metabolism and Nutrition Disorders           |
| Decreased appetite                            | 27.2 | 2.0 |
| Musculoskeletal and Connective Tissue Disorders |
| Musculoskeletal pain                          | 25.9 | 3.0 |
| Nervous System Disorders                     |
| Headache                                      | 19.9 | 0.4 |
| Distress                                      | 11.1 | 0.0 |
| Psychiatric Disorders                         |
| Insomnia                                      | 23.1 | 1.1 |
| Acute renal and Urinary Disorders            |
| Acute kidney injury                           | 17.1 | 1.1 |
| Respiratory, Thoracic and Mediastinal Disorders |
| Dysepsal                                      | 22.9 | 3.0 |
| Cough                                         | 13.9 | 0.0 |
| Vascular Disorders                            |
| Hypertension                                  | 14.9 | 5.0 |

*CID/EAE=Common Terminology Criteria for Adverse Events version 4.02

aAnemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normocytic normocytic anemia.

**Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.

Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection and neutropenic sepsis.

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

8.5 Genitourinary Use

In PRIMA, 39% of patients were aged ≥65 years and 10% were aged ≥75 years. In NOVA, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals could be ruled out.

8.6 Renal impairment

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

8.7 Hepatic impairment

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

8.10 OVERDOSAGE

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

17.1 PATIENT COUNSELING INFORMATION

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

Medication

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

Bone Marrow Suppression

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

Cardiovascular Effects

Advise patients to undergo blood pressure and heart rate monitoring at least weekly for the first two months, then monthly for the first year of treatment, and then periodically thereafter. Advise patients to contact their healthcare provider if blood pressure is elevated (see Warnings and Precautions (5.6)).

Dosage and Administration

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

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy (see Warnings and Precautions (5.10))

Contraception

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

Lactation

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

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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 56.
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The rapidly changing landscape of breast cancer therapies will be explored in depth during the upcoming 38th Annual CFS® conference in November. Tiffany A. Traina, MD, a breast cancer specialist who is cochairing the conference, discusses key developments in the field.

By ANDREW D. SMITH

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**ONCOLOGY BUSINESS MANAGEMENT**

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Community Practice Provides Model for Finding New Revenue in COVID-19 Era

By Barry Fortner, PhD

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Survey Results Find Insurance Coverage Is a Looming Crisis

By Keith A. Reynolds
Breast Cancer Care Turns Another Page

BY ANY MEASURE, the pace of discovery in medical oncology for breast cancer therapies has been remarkable. Over a period of less than 2 years, the FDA has approved 7 new drugs, expanded indications for 4 additional agents, and authorized 4 biosimilars and a new combination formulation of the longtime standby trastuzumab (Herceptin).

Such a robust lineup of new options would be noteworthy in any cancer type but is particularly intriguing in a malignancy that has been so extensively studied. It is heartening and humbling at the same time to realize that we still have so much to learn about breast cancer.

One interesting example of an area that is still evolving more than 20 years after trastuzumab became the first HER2-targeted therapy for breast cancer in 1998 is the concept of HER2 positivity. Of note, findings for the recently approved antibody-drug conjugate fam-trastuzumab deruxtecan-nxki (Enhertu) indicate that the drug not only is effective for patients with HER2-positive disease—it’s approved disease setting—but also for those with low HER2 expression.

The definition of HER2-low-expressing breast cancer most frequently used in clinical trials involves an immunohistochemistry (IHC) 1+ or IHC 2+ score along with a negative in situ hybridization (ISH) assay. That description differs from current guidelines that characterize HER2 positivity as IHC 3+ or gene amplification on an ISH assay on 1 or more tumor samples.

As it stands now, Tarantino et al report limited clinical value for administering trastuzumab to patients whose tests fall outside the boundaries of the standard measure of HER2 positivity. However, that might not always be the case. The new generation of therapies in development such as trastuzumab deruxtecan and others may be effective at a lower level of HER2 activity. If so, that could have profound implications for patients with breast cancer. As many as 55% of breast cancers express low levels of HER2 without gene amplification, Tarantino and colleagues note. Patients with these tumors currently are not candidates for HER2-positive therapies.

This development is just 1 of the nuances of the new breast cancer paradigm that is taking shape. In this issue of OncologyLive®, Tiffany A. Traina, MD, a cochair of the upcoming 38th Annual CFS® conference that Physicians’ Education Resource®, LLC (PER®) is hosting in November, is among the experts who provide insights into some of these questions. A more detailed look at emerging therapies is provided in the OncLive Peer Exchange® section.

We hope you enjoy reading about these new therapies. Please let our editorial director, Gina Columbus (gcolumbus@onclive.com), know what questions you would like us to explore in our publications and on OncLive.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
A new indication for CYRAMZA® (ramucirumab)

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PP-RB-US-3158  06/2020  © Lilly USA, LLC 2020. All rights reserved.
A recent article in *The New York Times Magazine* describes a provocative confrontation between a treating physician and a clinical investigator over the therapeutic course for a participant in a coronavirus disease 2019 (COVID-19) clinical trial at a New York hospital. Assuming the facts as stated in the article are accurate, the physician wanted to modify the blinded protocol-assigned treatment paradigm that, in her judgment, was failing to provide satisfactory results. In response, the research physician argued that scientific investigatory principles should be maintained: “Relying on gut instinct rather than evidence, he told them, was essentially ‘witchcraft.’”

This anecdote is striking because it so clearly lays out the often hidden truth related to potentially vastly different views on the role of a physician and their relationship with a patient versus the role of a clinical investigator and their relationship with a research subject participating in a therapeutic study. The physician, as depicted in this article, viewed the patient’s welfare as her major, if not sole, responsibility, whereas the investigator apparently felt a split loyalty to optimizing the patient’s care while also attempting to ensure as much as possible the fidelity of the ongoing research effort. At times, as highlighted in the article, those loyalties may be in substantial conflict. It is uncertain whether individuals who agree to participate in a therapeutic trial, particularly in potentially life-threatening situations, fully understand this highly relevant distinction.

Compounding this disquieting issue is the matter of assessing objectively the quality, optimal design, timeliness, and likelihood of completion and subsequent publication of many COVID-19 trials, also a concern regarding clinical studies in the oncology arena. This question is critical because patients who are asked to become research participants are specifically informed that a major—if not the major—purpose of their participation is to help develop generalizable knowledge that may be of relevance to future patients outside the investigative setting. If clinical trials in a given area are failing to achieve their prospectively stated accrual goals in a substantial percentage of cases, what does that say about the fundamental adequacy of the informed consent process?

Consider, for example, this observation reported in a recent peer-reviewed publication: Of 674 randomized trials involving COVID-19 infections listed on the ClinicalTrials.gov registry, 28.9% did not include a comparative control group that was either a formal placebo design or an acceptable standard of care. Of these trials, just 35.8% were multicenter, raising the question of the likelihood of whether many such studies would complete their accrual in a reasonably timely manner.

Further, and perhaps most remarkable, chloroquinines were being tested in 132 of 562 randomized studies (23.5%). Let me repeat that number so that the absurdity of the current state of affairs can be fully appreciated: There were 132 individual registered randomized trials examining a single drug (eg, hydroxychloroquine or chloroquine) in the management or prevention of COVID-19. And, if one solely examined prevention trials, a total of 86,950 participants would be needed for the registered studies examining chloroquine.

Is this a rational situation? How many of these studies will be completed and ultimately provide data that will
meaningfully affect the future treatment or prevention of COVID-19? Of course, asking this question is quite different from wondering how many of these studies will simply result in a peer-reviewed publication and subsequently adorn the résumé of the authors.

Significantly, the scientific community in the United Kingdom was able to initiate, complete, and report a landmark study related to the use of dexamethasone involving 6425 hospitalized patients randomized over a period of about 12 weeks. Investigators reported that the drug lowered 28-day mortality among patients receiving invasive mechanical ventilation or oxygen alone.³

By contrast, the massive resources of the United States have produced little more than a report about results of the uncontrolled use of convalescent plasma in at least 70,000 patients with COVID-19, leading to the conclusion that the strategy is reasonably safe and may provide some level of benefit to a poorly defined patient population.⁴,⁵

To be crystal clear, the successful conduct of randomized trials in this highly complex setting is difficult and will require major coordinated regional or national efforts; however, the United Kingdom’s scientific and regulatory communities have shown that this can be done. One would have hoped that relevant research, regulatory, and governmental communities bodies with essential representation from patients and their families in the United States could have worked together to quickly initiate and complete meaningful studies designed to thoroughly and objectively evaluate multiple strategies in different stages of the COVID-19 infectious process (eg, prophylaxis, early asymptomatic, mildly symptomatic nonhospitalized, hospitalized, intensive care admission, ventilator requirement, postacute infection) to answer critical questions relevant to all patients, whether they live in New York City, Los Angeles, or New Orleans.

Because it is likely that COVID-19 will be around for a considerable period of time, it is hoped that all involved in the clinical research establishment can view this experience as a process that needs substantial improvement.

Perhaps we can learn a lesson as we develop future real-world experience with anticancer strategies. For the benefit of all society, can we devise effective strategies to quickly initiate and complete high-priority oncology studies that answer clinically relevant questions across multiple geographies, patient demographic groups, and health care systems in a far more efficient manner than we do today?

REFERENCES
Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 3% 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 severe 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.

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.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in 7% 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.


Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 3 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.
1L CABOSUN TRIAL

The only TKI with superior PFS to sunitinib

**SINGLE-AGENT TKI OPTION**

**PRINCIPAL ENDPOINT IN CABOSUN**

**MEDIAN PFS**

<table>
<thead>
<tr>
<th>CABOMETYX</th>
<th>VS</th>
<th>sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.6 months (n=79)</td>
<td></td>
<td>5.3 months (n=78)</td>
</tr>
</tbody>
</table>

**52% reduction in risk of progression or death**

HR=0.48 (95% CI: 0.31-0.74), P=0.0008

CABOSUN was a randomized (1:1), open-label, multicenter, phase 2 trial of CABOMETYX vs sunitinib in 157 first-line patients with aRCC who had ≥1 IMDC risk factors.

2L METEOR TRIAL

The only TKI with superior OS in 2L aRCC

**SINGLE-AGENT TKI OPTION**

**SECONDARY ENDPOINT IN METEOR**

**MEDIAN OS**

<table>
<thead>
<tr>
<th>CABOMETYX</th>
<th>VS</th>
<th>everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.4 months (n=330)</td>
<td></td>
<td>16.5 months (n=328)</td>
</tr>
</tbody>
</table>

HR=0.66 (95% CI: 0.53-0.83), P=0.0003

METEOR was a randomized (1:1), open-label, phase 3 trial of CABOMETYX vs everolimus in 658 patients with aRCC who had previously received at least 1 prior anti-angiogenic treatment.

National Comprehensive Cancer Network (NCCN)*

**NCCN PREFERRED**

1L Cabozantinib (CABOMETYX) is the ONLY NCCN “PREFERRED” SINGLE-AGENT TKI OPTION for 1L intermediate/poor risk clear cell aRCC

2L Cabozantinib (CABOMETYX) is the ONLY NCCN “PREFERRED” SINGLE-AGENT TKI OPTION for 2L clear cell aRCC

As defined by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), preferred interventions are based on superior efficacy, safety, and evidence; and, when appropriate, affordability

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema, is diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most commonly reported (>25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

*Patients had ≥1 IMDC risk factors.
*PFS was assessed by a retrospective blinded IRC.
†≥1 prior anti-angiogenic therapy.
‡The primary PFS analysis was conducted in the first 375 subjects randomized to treatment.
§PFS was confirmed by blinded IRC.

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.


Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

CABOMETYX (cabozantinib) tablets 60 mg | 40 mg | 20 mg

Learn more at CABOMETYXhcp.com
CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION. PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION. INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

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

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal tract perforations, including fatal cases, 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 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% 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.

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 CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

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 diarrhea and then resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX. Discontinue CABOMETYX until improvement to Grade 1 and then 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, ostectomy, 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 treatment, and 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 for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

5.10 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed above and in the Warnings and Precautions section of the prescribing information: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR) and 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL). Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Adverse Reactions Leading to Permanent Discontinuation

- The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Leading to永久 Discontinuation in 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>Discontinuation in % of Patients</td>
<td>Percentage (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2-3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Exacerbation of hypertension, including Hypertension</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Nervous System</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Endocrine</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
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<tr>
<td></td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

*One subject randomized to everolimus received cabozantinib.

1 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
2 Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
3 Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash papulovesicular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculopapular, rash pruritic, contact dermatitis, dermatitis acneliform
4 Includes the following terms: hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation
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 ≥ 25% 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>Increased AST</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Increased triglycerides</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Increased GGT</td>
<td>25</td>
<td>7</td>
</tr>
</tbody>
</table>

Based on laboratory abnormalities.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CABOMETYX (n = 78)</th>
<th>Sunitinib (n = 72)</th>
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<tr>
<td></td>
<td>Grade 3-4</td>
<td>Grade 3-4</td>
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<td>Patients with any Grade 3-4 Adverse Reaction</td>
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<tr>
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<tr>
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<td>4</td>
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</tr>
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<td>Fatigue</td>
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<td>Metabolism and Nutrition</td>
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<td>Hypomagnesemia</td>
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<td>Hypophosphatemia</td>
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<td>0</td>
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<td>Hypertension</td>
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<td>3</td>
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<tr>
<td>Skin and Subcutaneous Tissue</td>
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<td></td>
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<tr>
<td>Palmar-plantar erythrodysthesia</td>
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<td>Weight decreased</td>
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<td>Increased AST</td>
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<td>Increased blood creatinine</td>
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<td>Thrombocytopenia</td>
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<td>11</td>
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<tr>
<td>Nervous System</td>
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<td>Syncope</td>
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<tr>
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</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Diaphonia</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Blood and Lymphatic</td>
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<tr>
<td>Anemia</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Psychiatric</td>
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<td>Confusional state</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Lung infection</td>
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<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<td></td>
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<tr>
<td>Back pain</td>
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<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>3</td>
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</tr>
<tr>
<td>Pain in extremity</td>
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<td>Anarthria</td>
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<td>Renal and Urinary</td>
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<td>Renal failure acute</td>
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<tr>
<td>Proteinuria</td>
<td>3</td>
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</tr>
</tbody>
</table>

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, open-label trial in patients with advanced hepatocellular carcinoma, in which 784 patients received 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.

### 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>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphonia</td>
<td>12</td>
<td>0</td>
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<tr>
<td>Endocrine</td>
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<td>Hypoalbuminemia</td>
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<td>Respiratory, Thoracic, and Mediastinal</td>
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<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>
Laboratory Abnormality | CABOMETYX N=467 | Placebo N=237 | Percentage of Patients
--- | --- | --- | ---
Chemistry | | | |
Increased LDH | 84 | 9 | 2 | 99%
Increased ALT | 73 | 12 | 37 | 60%
Increased AST | 73 | 24 | 46 | 19%
Hypokalemia | 51 | 1 | 32 | 1%
Increased ALP | 43 | 8 | 39 | 6%
Hypophosphatemia | 25 | 9 | 8 | 4%
Hyokalemia | 23 | 6 | 6 | 1%
Hypomagnesemia | 22 | 3 | 3 | 0%
Increased amylase | 16 | 2 | 9 | 2%
Hypocalemia | 8 | 2 | 0 | 0%
Hematologic | | | |
Decreased platelets | 54 | 10 | 16 | 0%
Neutropenia | 43 | 7 | 8 | 1%
Increased hemoglobin | 0 | 8 | 1 | 0%

Table 5. Laboratory Abnormalities Occurring in ≥ 5% of CABOMETYX-Treated Patients in CELESTIAL

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical 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 breastfeeding 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

Females and Males

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 (compared to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targetels were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cytic distalation 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, physeal 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 epidydimis/ testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSSUN and METEOR, 41% of 410 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 40% 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 disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to contact their healthcare provider if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistulas have been reported in patients taking CABOMETYX. Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their healthcare provider if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Nail and wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their healthcare provider for signs or symptoms of this condition.

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

Revision 02/2020

Distributed by Exelixis, Inc. Alameda, CA 94502

EXELIXIS

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Azacitadine Maintenance Therapy Gains Clearance for AML

Maintenance therapy with azacitidine tablets (Onureg) is now an available option for patients with acute myeloid leukemia (AML) who have achieved first complete remission or complete remission with incomplete blood count following intensive induction chemotherapy. The decision on the efficacy of the nucleoside metabolic inhibitor is based on data from the phase 3 QUAZAR AML-001 trial (NCT01757535), which showed that the oral formulation of azacitadine lengthened overall survival by 9.9 months with incomplete blood count following intensive induction chemotherapy. The FDA noted that significant differences in the pharmacokinetic parameters exist. As such, this product should not be substituted for intravenous or subcutaneous azacitidine; to do so, could lead to fatal adverse reactions. Further, the product has warnings and precautions for myelosuppression, increased early mortality in patients with other myelodysplastic syndromes and embryo-fetal toxicity.


Umbralisib Moves Toward Indication in MZL, Follicular Lymphoma

Umbralisib, a dual inhibitor of PI3K-δ and CK1-ε, received a priority review for patients with previously treated marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based treatment. The FDA also accepted a new drug application for umbralisib as a treatment for patients with follicular lymphoma (FL) who have received a minimum of 2 prior systemic therapies. A decision is expected from the FDA on the MZL indication by February 15, 2021. For the FL indication, which is under standard review, a decision is expected by June 15, 2021.

Umbralisib’s new drug application was based on findings from the single agent MZL and FL cohorts of the phase 2B UNITY-NHL study (NCT02793583). Topline results reported in October 2019 demonstrated that umbralisib achieved the primary end point of a target overall response rate of 40% to 50% in the FL cohort, which included 118 patients who received 2 or more prior lines of treatment, including an alkylating agent and a CD20-targeting monoclonal antibody. This end point was also met in the MZL cohort.

Follow-up is ongoing for mature overall response, duration of response, and safety analysis. Phase 3 trials of umbralisib are planned in MZL, as well as other subtypes of indolent non-Hodgkin lymphoma.


Myelopreservation Intervention Undergoes Review for SCLC

Trilaciclib, a CDK4/6 inhibitor administered prior to chemotherapy in patients with small cell lung cancer (SCLC) to reduce the risk of chemotherapy-induced myelosuppression, will receive a priority review for patients with SCLC who are being treated with chemotherapy. The FDA is scheduled to issue a decision on the agent’s new drug application by February 15, 2021.

Mechanistically, trilaciclib protects bone marrow and immune system function from treatment-related damage by arresting normal cells in the G1 phase of the cell cycle during exposure to chemotherapy. If approved, the therapy would be the first preemptively administered myelopreservation intervention available for this patient population and could reduce the need for rescue strategies such as growth factor administrations and blood transfusions.

To date, trilaciclib has been evaluated in 3 phase 2 studies in adults with extensive-stage SCLC: G1T28-02 (NCT02499770), G1T28-05 (NCT03041311), and G1T28-03 (NCT02514447). In an analysis of pooled trial data presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, investigators assessed the trilaciclib’s myelopreservation and antitumor effectiveness. When administered prior to chemotherapy, trilaciclib resulted in a significant decrease in most measures of multilineage chemotherapy-induced myelosuppression and the need for supportive care interventions. Data additionally showed that tumor responses were comparable between individuals who received placebo before chemotherapy (n = 119) and the 123 patients pretreated with trilaciclib.

TO READ MORE, VISIT https://bit.ly/3U1vdyZ.

Generic Pemetrexed Gets Green Light for Nonsquamous NSCLC

A generic form of pemetrexed (Alimta) for intravenous administration as a single-agent is now available for patients with locally advanced or metastatic nonsquamous non–small cell lung cancer (NSCLC) that has not progressed after 4 cycles of first-line platinum-based chemotherapy. The generic injection, which is a salt form version of Alimta, developed by Eli Lilly, has also been approved for use as a single-agent for recurrent, metastatic nonsquamous NSCLC in patients who received prior chemotherapy.

Pemetrexed was first approved on February 4, 2004, for use in combination with cisplatin for patients with malignant pleural mesothelioma. The recommended dose of pemetrexed is 500 mg/m² given as an intravenous infusion over 10 minutes on day 1 of each 21-day treatment cycle plus 75 mg/m² of cisplatin infused over the course of 2 hours starting 30 minutes following treatment with pemetrexed.


FoundationOne Liquid CDx Is Approved for All Solid Tumors

The FoundationOne Liquid CDx, a next-generation sequencing assay that analyzes more than 300 genes and gene signatures—such as microsatellite instability, in circulating tumor DNA from plasma—is approved for all solid tumors with multiple companion diagnostic indications. The plasma test will be covered across solid tumors for Medicare and Medicare Advantage beneficiaries, according to Foundation Medicine, FoundationOne Liquid’s developer. Notably, the approval included companion diagnostic indications for testing patients who are candidates for these therapies: rucaparib (Rubraca) for BRCA1/2-mutant metastatic castration-resistant prostate cancer; gefitinib (Iressa) for non–small cell lung cancer (NSCLC) that harbors EGFR exon 19 deletions; and osimertinib (Tagrisso) and erlotinib (Tarceva) for NSCLC tumors that have EGFR exon 21 L858R substitutions.

FoundationOne Liquid’s approval was based on analytical and clinical validation studies that collected more than 7500 plasma samples and 30,000 unique variants across more than 30 tumor types. When investigators analyzed the platform across malignancies, the testing showed high sensitivity and specificity, even at the low allele frequencies noted in the collected samples.


To date, trilaciclib has been evaluated in 3 phase 2 studies in adults with extensive-stage SCLC: G1T28-02 (NCT02499770), G1T28-05 (NCT03041311), and G1T28-03 (NCT02514447). In an analysis of pooled trial data presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, investigators assessed the trilaciclib’s myelopreservation and antitumor effectiveness. When administered prior to chemotherapy, trilaciclib resulted in a significant decrease in most measures of multilineage chemotherapy-induced myelosuppression and the need for supportive care interventions. Data additionally showed that tumor responses were comparable between individuals who received placebo before chemotherapy (n = 119) and the 123 patients pretreated with trilaciclib.
Relapsed/Refractory DLBCL Paradigm
Gains Chemotherapy-Free Option

by RACHEL NAROZNIAK, MA

TREATMENT OPTIONS FOR PATIENTS with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) now include an alternative to chemotherapy. On July 31, 2020, the FDA granted an accelerated approval to tafasitamab-cxix (Monjuvi) in combination with lenalidomide (Revlimid) for adults with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, who are not eligible for autologous stem cell transplant.

The regulatory decision was based on efficacy data from the phase 2 L-MIND trial (NCT02399085), which demonstrated a high overall response rate (55%; 95% CI, 43%-67%) and complete response rate (37%) in 71 patients with central pathology-confirmed DLBCL. Tafasitamab plus lenalidomide additionally induced partial responses in 18% of patients, with an acceptable safety profile. The median duration of response was 21.7 months.

In an interview with OncologyLive®, Kami J. Maddocks, MD, a professor of clinical internal medicine in the Division of Hematology at The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute in Columbus, discussed the regimen’s tolerability and promise for greater efficacy and more durable responses than the combination chemotherapy historically offered in the relapsed or refractory DLBCL second-line setting.

Please describe the patient population for which the combination is indicated and the efficacy data that led to the approval.

Tafasitamab and lenalidomide was studied in patients with relapsed diffuse large B-cell lymphoma who were not candidates for autologous stem cell transplant. This tends to be 2 populations of patients: those who, at their first relapse, are not candidates for autologous stem cell transplant, either because of age or comorbidities, or patients who are receiving salvage chemotherapy with the intent for transplant but do not respond well enough to that treatment to proceed to autologous stem cell transplant.

The combination therapy had an overall response rate of nearly 60% (58.8%) in this population of patients with relapsed diffuse large B-cell lymphoma, including a complete remission rate of a little over 40% (41.3%) (according to data from a long-term analysis of the L-MIND study announced by MorphoSys in May).

These responses proved durable, with a median progression-free survival of 16.2 months and a median duration of response of almost 3 years.

Mechanistically, how do these agents induce their anticancer activity?

These are 2 immunotherapies. Tafasitamab is an antibody to CD19, which is expressed on B cells throughout development, including high expression on malignant B cells, which preserve that expression even after patients received prior therapy. Lenalidomide is an oral immunomodulating agent with activity in a number of lymphomas, including diffuse large B-cell lymphoma. Preclinical data supported the potential synergy of the 2 agents with natural killer cell ADCC [antibody-dependent cellular cytotoxicity] enhanced with the combination of lenalidomide and tafasitamab.

What do we know about the regimen’s tolerability?

When you look at the combination of tafasitamab and lenalidomide, the toxicities that we see are very similar to those with lenalidomide alone. A small number of patients had infusion reactions from tafasitamab, but these were all grade 1 and easily managed. The most common adverse events with the combination were cytopenias—neutropenia, anemia, thrombocytopenia, and febrile neutropenia—and diarrhea, fatigue, and cough, with the most common serious adverse events being infections and febrile neutropenia. The incidence and severity of adverse events did improve in patients who were on tafasitamab monotherapy after 12 cycles of the combination, suggesting that the many, not all, toxicities were attributable to the lenalidomide.

This is the first second-line therapy to be OK’d for relapsed DLBCL. What does this combination’s approval mean for the paradigm?

This combination offers a great option for patients who relapsed from diffuse large B-cell lymphoma and are not candidates for autologous stem cell transplant. Prior to this approval and historically, we would typically offer these patients another chemotherapy regimen that was considered palliative and would be associated with many of the same toxicities as initial chemotherapy. This approval gives patients an opportunity to receive a non–chemotherapy-based treatment that appears to be more effective than administering any of these palliative chemotherapy options, with the potential for durable remissions. It also offers a different toxicity profile from that seen with chemotherapy options.

What are the next steps for this regimen?

A phase 1 trial [NCT04134936] evaluated tafasitamab or tafasitamab and lenalidomide in addition to R-CHOP [rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone] for the frontline treatment of diffuse large B-cell lymphoma. There is a randomized phase 3 trial planned to evaluate this combination in addition to R-CHOP versus the standard of care, R-CHOP alone.

It is likely to be investigated further in relapsed disease, maybe in other populations of relapsed patients or potentially with other combinations of both chemotherapy and nonchemotherapeutic agents that have activity in diffuse large cell lymphoma.

REFERENCE

PIVOTAL CLINICAL TRIAL

L-MIND (NCT02399085), a multicenter, single-arm trial, enrolled 81 patients with relapsed or refractory DLBCL who received 1 to 3 prior systemic therapies, including a CD20-directed cytolytic antibody, and were not candidates for high-dose chemotherapy followed by autologous stem cell transplantation. Seventy-one patients received the combination regimen, which consisted of 12 mg/kg of tafasitamab with 25 mg of lenalidomide on days 1 through 21 of each 28-day cycle, for a maximum of 12 cycles, followed by tafasitamab monotherapy.

BASELINE PATIENT CHARACTERISTICS

(N=71)

<table>
<thead>
<tr>
<th>Reason for ASCT ineligibility</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>13%</td>
</tr>
<tr>
<td>Refractory to salvage chemotherapy</td>
<td>47%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>27%</td>
</tr>
<tr>
<td>Refusal of high-dose chemotherapy/ASCT</td>
<td>13%</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplantation.

Prior systemic therapies (%)

- 1 prior line of therapy: 49%
- 2-4 prior lines: 51%

Refractory status (%)

- Refractory to prior therapy: 45%
- Refractory to rituximab: 42%

FDA approval—July 31, 2020

The FDA grants accelerated approval to tafasitamab-cxix in combination with lenalidomide (Revlimid) for adults who have relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low-grade lymphoma, and are not eligible for autologous stem cell transplant.

Mechanism of action:
- Tafasitamab is an Fc-modified monoclonal antibody that binds to CD19 antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including DLBCL.
- Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties.

How supplied:
- Tafasitamab
  - 200-mg lyophilized powder in a single-dose vial

Lenalidomide
- 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules

Dosing:
- 12 mg/kg of tafasitamab based on body weight administered as an intravenous infusion in combination with 25 mg of lenalidomide for a maximum of 12 cycles, followed by tafasitamab monotherapy until disease progression or unacceptable toxicity

Company: Tafasitamab: MorphoSys US Inc
Lenalidomide: Celgene

Efficacy Results in the L-MIND Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tafasitamab + lenalidomide followed by tafasitamab monotherapy (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best ORR (95% CI)</td>
<td>55% (43%-67%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>37%</td>
</tr>
<tr>
<td>Partial response rate</td>
<td>18%</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>21.7 (0-24.0)</td>
</tr>
</tbody>
</table>

ORR, overall response rate.

Warnings and Precautions

- Infusion-related reactions
- Myelosuppression
- Infections
- Embryo-fetal toxicity

Commonly Reported Adverse Events in the L-MIND Study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Tafasitamab + lenalidomide followed by tafasitamab monotherapy (N = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51.0% 49.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38.0% 3.7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>36.0% 7.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36.0% 1.2%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31.0% 17.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>26.0% 1.2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24.0% 1.2%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24.0% 0%</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>24.0% 4.9%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22.0% 0%</td>
</tr>
</tbody>
</table>
TOP TWEETS

@OncLive
WATCH: @AndreGoyMD of @JTCancerCenter, discusses the risk assessment of DLBCL and prognostic and predictive significance of genetic signatures. #lymsm

@OncLive
Immunotherapy, PARP inhibitors, and ADCs have become pillars of treatment in TNBC. @BurrisSkip @SarahCannonDocs #bcsm

@OncLive
In light of the #COVID-19 pandemic, many have learned to adapt and develop new strategies to best care for patients with prostate cancer while preventing the spread of the virus. @qtdrinth @DanaFarber #pcsm

@OncLive
Drug Repositories Aim to Solve Access Issues @OSUCCC_James

@OncLive
@US_FDA Grants Trilaciclib Priority Review for Small Cell Lung Cancer #ksm

MORE ONLINE twitter.com/OncLive

ONCLIVE® ONAIR PODCAST SPOTLIGHT

FDA APPROVAL INSIGHTS B Rexucabtagene autoleucel in Relapsed/Refractory MCL

Michael Wang, MD, a professor in the department of lymphoma and myeloma in the division of cancer medicine at The University of Texas MD Anderson Cancer Center in Houston, discusses the approval of brexucabtagene autoleucel (Tecartus; formerly KTE-X19), in relapsed/refractory mantle cell lymphoma (MCL), findings from the phase 2 ZUMA-2 trial (NCT02601313) that led to the approval, and ongoing research with the agent.


MARVELS IN MEDICINE Brau nstein breaks down Top ASCO 2020 Abstracts in Myelo ma

Marc J. Braunstein, MD, PhD, canvases some of the most noteworthy data presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program across the first-line and relapsed/refractory settings in myeloma. The use of triplet and quadruplet regimens, novel agents, and cellular therapies are on the menu of therapeutic topics covered by Braunstein, codirector of the autologous stem cell transplant program at NYU Winthrop Hospital of NYU Langone Health’s Perlmutter Cancer Center in Mineola, New York.

LISTEN: https://bit.ly/2Y1wQjP

RESEARCH REFLECTIONS Jordan on undertaking an unanticipated career in breast cancer

V. Craig Jordan, CMG, OBE, PhD, DSc, FMedSci, “The Father of Tamoxifen,” details his work with British Special Forces during the Cold War and recounts the story of how his career in science started with a spark—one that set his parents’ house on fire. Jordan is a professor of breast medical oncology and molecular and cellular oncology at The University of Texas MD Anderson Cancer Center in Houston.

LISTEN: https://bit.ly/2E3qEX3

TALKING TUMORS Discussing KRAS-targeted therapy in NSCLC with Riess

Jonathan W. Riess, MD, MS, tackles KRAS-directed treatment strategies in non–small cell lung cancer, such as KRAS G12C inhibitors. Riess, an associate professor of medicine in the division of hematology and oncology at the University of California Davis Comprehensive Cancer Center, additionally addresses preliminary safety and efficacy data with AMG 510, and research into commutations that could further refine the potential role of the agent in the KRAS-mutant space.

LISTEN: https://bit.ly/3jomZme

SPOTLIGHT

Tripathy navigates ever-changing HER2+ breast cancer treatment landscape

The HER2-positive breast cancer treatment paradigm is constantly changing, explained Debu Tripathy, MD. Tripathy notes that in the past year, there have been 2 exciting drug approvals: tucatinib (Tucysa) and fam-trastuzumab deruxtecan-nki (Enhertu). “Trastuzumab deruxtecan may be able to impact neighboring cells, which is very important. I believe that, after progressing on T-DM1 [ado-trastuzumab emtansine] and receiving trastuzumab deruxtecan instead, we may not go back to T-DM1.”

READ MORE: https://bit.ly/3j3RI71
For breaking news, interviews with key opinion leaders, conference coverage, and more, follow us on Twitter, @OncLive, or use your smartphone to scan this QR code.

HOW DNA MEDICINES COULD TRANSFORM TREATMENT OF Glioblastoma Multiforme

Better technology is rekindling the promise of DNA medicines in oncology, including the treatment of glioblastoma. Contrary to popular opinion, DNA medicines are not synonymous with “gene therapy,” but they have been challenged by the same biases and presumptions, and because of that, DNA medicines have failed to gain therapeutic ground in the treatment of human disease. Until now.

A recent resurgence of DNA medicines is due in large part to improvements in the technology that have enabled their reintroduction into the clinic. Although several treatments have recently made their way to the clinic, patients with glioblastoma still await a new therapy that can harness the power of the human immune system. INO-5401, a DNA medicine that is made up of 3 synthetic DNA plasmids encoded for human telomerase, Wilms Tumor 1 protein, and prostate-specific membrane antigen, developed by Inovio, may be the answer.

READ MORE: https://bit.ly/3gfHu1H

ONCLIVE® VIDEOS

HAMILTON ON THE EFFICACY OF TRASTUZUMAB DERUTEXECAN IN HER2-LOW BREAST CANCER

Impressive response rates have been reported with fam-trastuzumab derutexan-nxki (Enhertu) in HER2-low-expressing breast cancers, according to Erika P. Hamilton, MD, director of the Breast Cancer and Gynecologic Cancer Research Program at the Sarah Cannon Research Institute in Nashville, Tennessee. Although further study will be necessary to determine whether the agent has a role in HER2-low-expressing disease, the unique mechanism of action of trastuzumab derutexan bolsters the case for its use in this subset, Hamilton said.

VIEW VIDEO: https://bit.ly/3iXpqE0

RAPID READOUTS: FINDINGS FROM MYELOMA STUDY

Cristina Gasparetto, MD, discusses initial findings from the phase 3 BOSTON study (NCT03110562), which demonstrated that selinexor (Xpovio) in combination with bortezomib (Velcade) and low-dose dexamethasone improved median progression-free survival over standard bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma. Investigators tested the triplet regimen in patients who received 1 to 3 prior anti–multiple myeloma regimens. Gasparetto is a professor of medicine at Duke University School of Medicine in Durham, North Carolina.

VIEW VIDEO: https://bit.ly/32h88m6

MESIA ON DEVELOPING RACIALLY INCLUSIVE CLINICAL TRIALS IN MPNs

While significant work is needed to develop racially inclusive clinical trials, ongoing efforts to balance racial patient populations are worthwhile and could result in more broadly applicable data in myeloproliferative neoplasms, according to Ruben A. Mesa, MD, director of the Mays Cancer Center at UT Health San Antonio MD Anderson Cancer Center in Texas. Teamwork is critical to diversifying clinical trials and will require collaboration between FDA stakeholders, pharmaceutical representatives, medical community members, academic centers, third-party payers, and patient advocacy groups.

VIEW VIDEO: https://bit.ly/3gigcYB

NOTABLE QUOTABLES

“I always say ‘What’s the point of having your myeloma be in remission, but you’re chained to the infusion center all the time?’ [With subcutaneous daratumumab] we basically have comparable efficacy with what appears to be an improved safety profile, with lower rates of infusion-related reaction; obviously, [it is] way more convenient.”

—Ajai Chari, MD

Director of clinical research, multiple myeloma program; associate director of clinical research, Cancer Clinical Trials Office; professor of medicine, hematology/oncology, Icahn School of Medicine, Mount Sinai

READ MORE: https://bit.ly/34j1BtJ
COVID-19 Registry Data Show Increased Mortality in Patients With Cancer

by KRISTI ROSA

**THE CORONAVIRUS DISEASE 2019** (COVID-19) mortality rate appears to be higher in patients with cancer compared with that of the general population, according to updated data reported during the American Association for Cancer Research (AACR) Virtual Meeting: COVID-19 and Cancer, and several factors associated with mortality are emerging.

“Several ongoing registries are collecting a wealth of data on patients with cancer who have COVID-19, and we’re starting to see data [from these efforts reported]. The COVID-19 mortality rate in patients with cancer appears to be higher than that of the general population,” Brian I. Rini, MD, professor of medicine and chief of clinical trials at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, said during a presentation at the meeting.

Data have additionally indicated that patients with lung cancer may have a higher COVID-19 mortality rate versus patients with other kinds of cancers: “Specifically, [mortality] was 16% per the most recent update from the COVID-19 and Cancer Consortium [CCC19], and patients with lung cancer appear especially vulnerable, according to data from TERAVOLT,” Rini said. “Several factors relating to COVID-19 mortality in patients with cancer are also being reported; some are cancer related, such as the status of their cancer and perhaps performance status, and others are unrelated, such as age or gender.”

In his presentation, Rini summarized the registries collecting data regarding COVID-19-associated mortality in patients with cancer, shared available clinical insights, and highlighted a new study that will provide longitudinal data on a large cohort of patients with active cancer currently receiving treatment (FIGURE 1).

**CCC19**

Early on in the COVID-19 pandemic, many investigators hypothesized that patients would be at increased risk of virus-related adverse outcomes because of advanced age, presence of comorbidities, increased contact with the health care system, immune alterations due to their cancer and/or treatment, and decreased performance status, according to Rini.

CCC19 started as a grassroots effort designed to collect granular data on patients with cancer and their outcomes with the virus. The effort has since grown tremendously, with more than 114 participating institutions to date.

The initial analysis of registry data was presented during the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program by Jeremy L. Warner, MD, MS, an associate professor of medicine in the Division of Hematology and Oncology and of biomedical informatics at Vanderbilt University. Findings showed that patients with progressive cancer were 5.2 times more likely to die within 30 days of receiving a COVID-19 diagnosis versus patients in remission or without any evidence of disease.

Additionally, the risk of death was found to be 1.79 times greater for patients with stable cancer versus those with no evidence of disease. The data were simultaneously published in The Lancet.

During the 2020 AACR Virtual Meeting: COVID-19 and Cancer, Rini reported an update based on the third data lock on June 26, 2020. At that time, 2956 surveys had been submitted to the registry. After certain surveys were excluded, investigators analyzed data from 2749 patients.

Results showed that at a median follow-up of 30 days, the mortality rate was 16% (n = 433). Notably, the rate reported in the initial analysis was 13%, according to Rini. Some of the major...
outcomes measured included mechanical ventilation (12%) and intensive care unit (ICU) admission (16%). The composite outcome rate, defined as death, severe illness requiring hospitalization, ICU admission, or mechanical ventilation, was 29%. Moreover, almost half the patients required oxygen (45%) and the majority (60%) were hospitalized.

When looking at mortality for select patient subgroups, the rate of mortality per global statistics was 5%. Notably, patients who had an ECOG performance status of 0 and no comorbidities had a relatively low mortality rate (4%). However, investigators observed “an increasing mortality rate for men, those with progressing cancer, older patients, and those with worse performance status,” Rini said. “If you combine these adverse risk factors, you get into very high mortality rates.”

Regarding cancer-specific mortality, breast cancer had the largest cohort of patients (n = 502) but the lowest mortality rate, at 8%. Higher mortality rates were observed in patients with lymphoma (22%; n = 263), plasma cell dyscrasias (19%; n = 137), colorectal cancer (19%; n = 186), and prostate cancer (18%; n = 392). Patients with lung cancer (n = 237) had the highest mortality rate, at 26%.

Investigators also collected data on some of the factors associated with 30-day mortality. Updated data, which differed from what The Lancet originally published, revealed that non-Hispanic Black patients had a higher risk than White patients. Hematologic malignancies have also become a significant factor, with an adjusted odds ratio (AOR) of 1.8 compared with solid tumors. “You also see a worsening performance status for a cancer that is present or is certainly progressing, increasing a patient with cancer’s risk of dying from COVID-19,” Rini added.

Certain factors did not reach statistical significance, including obesity (AOR, 1.23), cytotoxic chemotherapy versus none (AOR, 1.14), noncytotoxic therapy versus none (AOR, 0.75), and recent surgery (AOR, 1.05). “In the present analysis of almost 3000 patients, I think this provides reassurance that cancer care can and should continue for these patients,” Rini said.

**TERAVOLT**

A separate global registry, TERAVolt (Thoracic canCers international coVid 19 cOLlaboraTion), collects data on patient characteristics and outcomes among individuals with thoracic cancers and COVID-19. The initiative is led by Leora Horn, MD, MSc, the Ingram Associate Professor of Cancer Research and clinical director of the Thoracic Oncology Program at Vanderbilt-Ingram Cancer Center; and Marina Chiara Garassino, MD, a medical consultant in the Medical Oncology Division at Fondazione IRCCS Istituto Nazionale dei Tumori and head of the Simple Structure of Thoraco-Pulmonary Medical Oncology at the IRCCS National Cancer Institute Foundation, both in Milan, Italy.

Data reported from 400 patients in the TERAVolt database showed a very high mortality rate of 35.5%, with 78.3% of patients requiring hospitalization and 8.3% admitted to the ICU. “Many of the patients in this registry were from Italy at the time of their crisis, and so they may not have had access to ICU admission; however, I think the high mortality rate seen in CCC19 is also reinforced here,” Rini explained.

**FIGURE.** The Oncology Community Takes Aim at COVID-19 With Data-Collecting Initiatives

A global consortium developed to amassed data on COVID-19’s impact on patients with thoracic cancers, irrespective of prior therapy. Designed to measure the impact of COVID-19 infection on the delivery of cancer care and the pattern of symptoms and severity of the respiratory virus, this registry collects baseline and follow-up patient data, which will be analyzed in periodic reports.

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A consortium of more than 120 cancer centers collaboratively collecting prospective, granular data about patients with cancer and COVID-19.
In a multivariate analysis of risk factors linked with death from COVID-19, investigators also reported older age (HR, 1.70) and worsening performance status (HR, 2.14) as adverse risk factors. Receiving steroids prior to COVID-19 diagnosis was determined to be of borderline significance (HR, 1.49), and, when looking at oncologic therapy, investigators noted that receiving chemotherapy versus other types of treatment was another significant risk factor.

**EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY–COCARDE**

The European Society for Medical Oncology–Cocarde registry, an international collaborative project launched to rapidly gather data from health care professionals on treatment approaches focuses on the impact of COVID-19 in patients with cancer with suspected or confirmed infection. To be eligible for inclusion, patients must have a solid or hematologic malignancy and laboratory-confirmed or clinical diagnosis of COVID-19. The exploratory end points include major demographic features of patients with cancer and COVID-19, prevalence of major comorbidities in this patient population, the proportion of patients with cancer who experience a severe event overall, the proportion of patients with cancer and COVID-19 who received systemic treatment in the last 2 months prior to infection, risk factors predictive of severe clinical course, biomarkers predictive of cancer treatment-specific adverse effects, prognostic factors, and cancer- and COVID-19–specific mortality.

“This registry is just up and running; it has not yet reported data,” noted Rini.

**AMERICAN SOCIETY OF HEMATOLOGY RESEARCH COLLABORATIVE COVID-19 REGISTRY FOR HEMATOLOGY**

The American Society of Hematology Research Collaborative COVID-19 Registry for Hematology represents another ongoing data-aggregating effort. The registry is intended to serve as a global public reference tool to capture information on patients with hematologic malignancies who test positive for COVID-19 and experience a post-COVID-19 hematologic complication.

Interestingly, as data are input into the platform, real-time observational summaries are produced and made available.

“Top-line data show a fairly high mortality rate. Although this is a small number of patients, it again reinforces with new findings from CCC19 [that] hematologic malignancies can be a risk factor,” Rini said.

**ASCO SURVEY ON COVID-19 IN ONCOLOGY REGISTRY**

ASCO has also launched a registry that aims to promote a better understanding of patterns in symptoms and severity of COVID-19 in patients with cancer and, importantly, the impact of the virus on delivery of cancer care and patient outcomes. The registry will collect baseline and follow-up data on how COVID-19 affects care for this patient population through the pandemic and into 2021.

Specifically, the data will include treatment approaches, cancer status, changes to cancer evaluation and treatment plans in patients infected with the virus, status of infection, and cancer.

As of June 25, 2020, 37 practices in 22 states were enrolled, with baseline data available for 131 patients.

“What’s different about the ASCO registry is that it is looking in a more granular way at the delivery of cancer care compared with the other registries that I have discussed so far,” Rini said. “Are patients having delay of cancer care? Are they having avoidance of cancer care? Is this about the delivery of care as much as the outcomes of COVID-19 infection in this population.”

**LAUNCH OF NCCAPS: A NATURAL HISTORY STUDY**

In the National Cancer Institute COVID-19 in Cancer Patients Study (NCCAPS; NCT04387656), investigators will follow patients and collect medical and other data over time to learn more about the virus and its symptoms. Through the NCCAPS initiative, investigators hope to help the cancer community better manage patients with cancer who are infected with the virus in the future.

To be eligible for the study, patients must be receiving active treatment for metastatic cancer within the past 6 weeks, including chemotherapy, immunotherapy, treatment with monoclonal antibodies, targeted therapies, endocrine therapy, or radiation therapy. Prior neoadjuvant or adjuvant treatment for nonmetastatic stage I to III disease received within the past 6 weeks; prior allogeneic stem cell transplant or chimeric antigen receptor T-cell or other modified cellular therapy, completed anytime; active treatment or prophylaxis for graft-versus-host disease; or autologous bone marrow transplant within the past 2 years are all permitted.

Investigators plan to accrue 2000 patients and follow outcomes for up to 2 years. Data will be collected on preexisting comorbidities, cancer type and treatment, demographic factors, COVID-19 course, short- and long-term cancer outcomes, and any modifications made to cancer treatment.

“There’s also a large effort being made to collect imaging scans just prior to COVID-19 diagnosis and what would be done normally for cancer staging or during the course of caring for patients for COVID-19,” Rini said. “The unique, special part of this study is that biospecimens are being collected, and we’ll look at serology, such as the development of antibodies over time, cytokine abnormalities—especially in patients who have more acute inpatient courses—and DNA-based genome-wide association studies, as well as coagulation parameters.”

The study has been activated at over 500 sites, Rini said, adding that accrual began a few weeks prior to his AACR presentation. “[Investigators expect NCCAPS to] accrue rapidly over the next several months,” Rini concluded.
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NEARLY 15 YEARS have passed since pathologists at Memorial Sloan Kettering Cancer Center (MSK) conducted gene expression analyses on breast cancer primary tumors and described a potential role for a novel target, which quickly became a major research focus for their colleague Tiffany A. Traina, MD.

Investigators found that a significant number of the hormone receptor-negative samples they examined demonstrated androgen receptor (AR) pathway activity. The discovery suggested that androgen-targeting strategies developed to treat prostate cancer might also benefit a subset of women with breast cancer, and Traina was eager to investigate. After years of work in this area, she is poised to co-lead the first randomized trial comparing the AR inhibitor enzalutamide (Xtandi) versus chemotherapy in patients with triple-negative breast cancer (TNBC) through the Translational Breast Cancer Research Consortium.

Androgen deprivation strategies are just 1 area of research interest for Traina, a medical oncologist at MSK in New York, who specializes in the exploration of novel targeted therapies for TNBC. Clinical investigations are, in turn, just part of a career that includes a full practice, leadership roles at MSK and the American Society of Clinical Oncology, and a commitment to sharing her knowledge with other physicians, both at MSK and at professional conferences around the world.

In November, Traina will cochair the 38th Annual CFS® conference, which is hosted by Physicians’ Education Resource®, LLC (PER®). The 3-day event will take place November 4 through November 6 and feature live, interactive virtual presentations on the practice-changing innovations in cancer diagnosis, treatment, and supportive care that occurred over the past year.

Traina is organizing the sessions with her cochairs, Benjamin P. Levy, MD, and William K. Oh, MD. Levy is clinical director of medical oncology at Johns Hopkins Sidney Kimmel Cancer Center in the DC Region, and Oh is chief of hematology and medical oncology and deputy director at The Tisch Cancer Institute at Icahn School of Medicine at Mount Sinai in New York, New York.

The conference provides clinically useful insights into best practices and emerging approaches for a broad range of cancer types, including hematologic malignancies, genitourinary cancers, and lung cancers. The agenda also will feature a section on the impact of the coronavirus 2019 disease (COVID-19) in oncology.

This year’s CFS® will be particularly provocative for breast cancer. “There were a few areas within breast cancer that saw really exciting advances over the past year or so, and they will naturally be major areas of focus for the symposium,” Traina said in an interview with OncologyLive®.

“First, in the space of women with HER2-positive advanced breast cancer, we’ve seen 2 new agents approved by the FDA since December 2019. These have both produced impressive efficacy results and offer valuable new options for our patients with HER2-positive disease,” she said, referring to fam-trastuzumab deruxtecan-nxki (Enhertu) and tucatinib (Tukysa).

“The other area with significant advances for review is triple-negative breast cancer,” Traina said. “The FDA has approved use of a novel antibody-drug conjugate [ADC] for patients with metastatic TNBC being treated in the third line or later [sacituzumab govetecan-hziy; Trodelvy]. This is

by ANDREW D. SMITH
an area of tremendous unmet need, with often short duration of response and poorer outcome with conventional chemotherapies. Additionally, we’re seeing an expanded role for immunotherapy in triple-negative breast cancer, both in the early-stage setting and in first-line metastatic disease.”

Traina’s expertise in translating such research developments into clinical practice also will be integrated into the breast cancer discussions, where she will serve as a moderator. “Tiffany is a respected colleague and a thought leader in triple-negative breast cancer,” said Shalu Modi, MB, a medical oncologist at MSK who has worked with Traina on several studies. “She has led the pioneering studies of androgen receptor-expressing triple negative breast cancer, and she manages a diverse portfolio of novel agents focused on this subtype of aggressive cancer.”

NEW HER2-POSITIVE OPTIONS ABOUND

The recent spate of breast cancer advancements began in December 2019, when the FDA accelerated approval of trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior HER2-targeting therapies.2

Approval for trastuzumab deruxtecan, an ADC that combines an anti-HER2 antibody with a cytotoxic topoisomerase I inhibitor, hinged upon findings from the DESTINY-Breast01 trial (NCT03248492), which reported objective responses in 60.9% (95% CI, 53.4%-68.0%) of 184 heavily pretreated participants. The median response duration was 14.8 months (95% CI, 13.8-16.9), and the median duration of progression-free survival (PFS) was 16.4 months (95% CI, 12.7-not reached).3

Interestingly, trastuzumab deruxtecan also showed a high response rate among patients whose tumors had low expression of HER2 in data from a phase 1 trial (NCT02564900). In all, 20 (37%) of the 54 women who had low expression of HER2, defined as an immunohistochemistry score of 1+ or 2+ with negative in situ hybridization, responded to treatment.4

In April 2020, the FDA approved the oral tyrosine kinase inhibitor tucatinib for patients with advanced or metastatic HER2-positive breast cancer who have received at least 1 prior HER2-targeting regimen, based on results from the HER2CLIMB trial (NCT02614794), in which 612 patients were randomized to receive trastuzumab and capcitabine plus tucatinib or placebo.2

Median PFS in patients receiving tucatinib was 7.8 months (95% CI, 7.5-9.6) compared with 5.6 months (95% CI, 4.2-7.1) for patients enrolled in the control arm (HR, 0.54; 95% CI, 0.42-0.71; P < .001). Median overall survival (OS) in patients who received tucatinib was 21.9 months (95% CI, 18.3-31.0) compared with 17.4 months (95% CI, 13.6-19.9) for patients in the control arm (HR, 0.66; 95% CI, 0.50-0.88; P = .005).5

Tucatinib also has demonstrated efficacy in patients with brain metastases. Median PFS for patients with baseline brain metastases was 7.6 months with tucatinib (95% CI, 6.2-9.5) and 5.4 months with placebo (95% CI, 4.1-5.7), which translated into a 52% lower risk of disease progression or death (HR, 0.48; 95% CI, 0.34-0.69; P < .001).6

“We have these 2 powerful new agents to help improve outcomes for women with advanced HER2-positive breast cancer,” Traina said, adding that highly effective therapies for patients with brain metastases have been elusive. “CNS disease has posed a real clinical challenge.”

The FDA also expanded the indication of neratinib (Nerlynx), an orally available tyrosine kinase receptor inhibitor of EGFR, HER2, and HER4. The drug was previously approved in 2017 as monotherapy for extended adjuvant treatment of adults with early-stage HER2-positive breast cancer following trastuzumab (Herceptin)-based therapy.2

In February 2020, neratinib gained approval in combination with capecitabine for adults with advanced or metastatic HER2-positive breast cancer who have received 2 or more previous anti-HER2-based regimens in the metastatic setting.2

The new indication is based on findings from the phase 1/2 IMMU-132-01 trial (NCT01631552), in which sacituzumab govitacan demonstrated a response rate of 33.3% (95% CI, 24.6-43.1) and a median duration of response of 7.7 months (95% CI, 4.9-10.8) in a heavily pretreated population. Median PFS was 5.5 months (95% CI, 4.1-6.3), and median OS was 13.0 months (95% CI, 11.2-13.7).7

The randomized phase 3 ASCENT study (NCT02574455) testing sacituzumab govitacan versus physician’s choice demonstrated a statistically significant improvement in PFS with the neratinib combination compared with lapatinib (Tykerb) plus capecitabine (HR, 0.76; 95% CI, 0.63-0.93; P = .0059). The PFS rate at 18 months was 16.3% (95% CI, 11.3%-22.1%) for the neratinib arm compared with 7.4% (95% CI, 4.1%-12.0%) with the lapatinib regimen. The overall incidence of intervention for CNS disease also was lower with neratinib at 22.8% (95% CI, 15.5%-30.9%) versus 29.2% (95% CI, 22.5%-36.1%) for lapatinib (Gray’s test for equality, P = .043).8

RECENT APPROVALS BOLSTER TNBC LANDSCAPE

The treatment options for patients with TNBC also grew with the introduction of sacituzumab govitacan, an ADC that targets TROP-2. The FDA granted the agent an accelerated approval in April 2020 for patients with metastatic TNBC who have received 2 or more prior lines of therapy in the metastatic setting.2

The approval was based on findings from the phase 1/2 IMMU-132-01 trial (NCT01631552), in which sacituzumab govitacan demonstrated a response rate of 33.3% (95% CI, 24.6-43.1) and a median duration of response of 7.7 months (95% CI, 4.9-10.8) in a heavily pretreated population. Median PFS was 5.5 months (95% CI, 4.1-6.3), and median OS was 13.0 months (95% CI, 11.2-13.7).7

The randomized phase 3 ASCENT study (NCT02574455) testing sacituzumab govitacan versus physician’s choice...
chemotherapy (ie, eribulin, capcitabine, gemcitabine, or vinorelbine) in relapsed/refractory TNBC has been completed and results are expected at the Virtual 2020 European Society for Medical Oncology (ESMO) Congress.

Clinical trials of immunotherapy in TNBC have produced a mix of findings. Atezolizumab (Tecentriq), a PD-L1 immune checkpoint inhibitor (ICI), became the first immunotherapy approved for breast cancer in March 2019.

The FDA granted an accelerated approval for atezolizumab in combination with nab-paclitaxel (Abraxane) for patients with unresectable locally advanced or metastatic PD-L1-positive TNBC based on PFS findings from the IMpassion130 trial (NCT02425891). PD-L1 positivity was defined as staining on tumor-infiltrating cells of any intensity covering at least 1% of the tumor area.8

The median PFS with atezolizumab plus nab-paclitaxel was 7.4 months (95% CI, 6.6-9.2) compared with 4.8 months (95% CI, 3.8-5.5) for those receiving placebo with nab-paclitaxel (stratified HR, 0.60; 95% CI, 0.48-0.77; \( P < .0001 \)). The objective response rates were 53% versus 33% for the atezolizumab and the placebo-containing arms, respectively.8

However, data from the phase 3 IMpassion131 study (NCT03125902) evaluating atezolizumab in combination with paclitaxel failed to confirm a statistically significant PFS benefit compared with placebo plus paclitaxel in treatment-naïve patients with inoperable locally advanced or metastatic TNBC, according to Roche, the company developing the drug.9

There also was a negative trend for OS, although the study was not powered for this end point and the data were immature at the time of the analysis, Roche said. Full findings from trial are being discussed with global health authorities and are planned for presentation at the Virtual 2020 ESMO Congress.9

On September 8, the FDA issued an alert advising providers not to substitute paclitaxel for nab-paclitaxel in clinical practice and noted that the combination of atezolizumab plus paclitaxel is not an approved use for patients with breast cancer. The agency also said continued approval of atezolizumab plus nab-paclitaxel may be contingent upon findings from additional clinical trials.10

Traina said she would have to examine the findings before forming an opinion about the results of IMpassion131. “We haven’t seen the data yet and haven’t had an opportunity to really dive into the details for a greater understanding of how trial design and population differences may account for the unexpected outcome,” she said. “We are certainly trying to understand why the earlier IMpassion study partnered with nab-paclitaxel was a positive trial and this one missed its primary end point.”

**EARLIER USE OF ICI THERAPY SHOWS BENEFIT**

Nevertheless, ICIs are displaying positive signals in earlier disease settings. Results from the phase 3 IMpassion031 trial (NCT03197935) showed a statistically significant and clinically meaningful improvement in pathological complete response (pCR) for atezolizumab as neoadjuvant therapy combined with nab-paclitaxel, followed by doxorubicin and cyclophosphamide, compared with chemotherapy plus placebo in patients with early-stage TNBC.11

The benefit was observed regardless of PD-L1 expression, according to Genentech, a member of the Roche Group. Findings are planned for presentation at the Virtual 2020 ESMO Congress and will be discussed with the FDA and other regulatory authorities, the company said.11

In the KEYNOTE-355 trial (NCT02819518), patients with previously untreated, locally recurrent, inoperable or metastatic TNBC were randomized to receive pembrolizumab (Keytruda), a PD-1 inhibitor, plus chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) or placebo plus chemotherapy. Results were stratified by combined positive score (CPS) of the number of PD-L1-positive tumor cells, lymphocytes, and macrophages divided by the total number of tumor cells multiplied by 100.12

For participants with a CPS of 10 or more, the median PFS for the pembrolizumab regimen was 9.7 months compared with 5.6 months for chemotherapy alone (HR, 0.65; 95% CI, 0.49-0.86; \( P = .0012 \)). For those with a CPS of less than 10, median PFS was 5.8 months with the pembrolizumab combination versus 5.7 months with chemotherapy alone (HR, 0.94; 95% CI, 0.76-1.16).12

Investigators said the findings show the potential for adding pembrolizumab to first-line TNBC therapy. The FDA has granted a breakthrough therapy designation for pembrolizumab plus chemotherapy as neoadjuvant treatment for patients with high-risk, early-stage TNBC.12

Additionally, pembrolizumab plus
chemotherapy demonstrated promising results as neoadjuvant therapy in the I-SPY 2 trial (NCT01042379) in patients with early-stage, high-risk hormone receptor-positive/HER2-negative breast cancer or TNBC. Final estimated pCR rates were 44% versus 17%, 30% versus 13%, and 60% versus 22% for pembrolizumab plus neoadjuvant chemotherapy compared with standard neoadjuvant chemotherapy in the HER2-negative, hormone receptor-positive/HER2-negative, and TNBC cohorts, respectively.11

Traina believes that recent study findings are charting an effective course for ICI therapy in the treatment paradigm. “I think we’ve come to see that for select patients with metastatic TNBC, introducing these agents early in the first-line setting has greater promise than using them in a later line,” she said. “We are also now seeing from early-stage trials that moving these checkpoint inhibitors up into the neoadjuvant setting, even potentially the adjuvant setting, may have meaningful benefit.”

**NOVEL APPROACHES DRAW TRAINA’S INTEREST**

In her research, Traina focuses on investigating novel therapeutic strategies and targeted therapies to treat TNBC. Early in her career, she was among MSK investigators who established that a dose-dense adjuvant chemotherapy regimen, delivered at shorter intervals than the conventional time frame, is tolerable and feasible.14

Under the mentorship of Clifford A. Hudis, MD, and Larry Norton, MD, a 2016 Giants of Cancer Care® award winner, Traina helped develop a 7 days on, 7 days off dosing schedule for capecitabine that allows for higher doses with decreased gastrointestinal toxicities than conventional 14-day continuous dosing.15,16

Her current projects include testing patritumab deruxtecan (U3-1402), a HER3-directed ADC, in patients with HER3-positive metastatic TNBC; evaluating durvalumab (Imfinzi) plus olaparib (Lynparza) in TNBC; and studying postoperative atezolizumab therapy plus chemotherapy in patients with stage II or III TNBC.

Traina is particularly enthusiastic about the prospect of conducting further studies into the potential for AR-directed strategies in TNBC. In 2018, Traina and colleagues...
reported that patients with locally advanced or metastatic AR-positive TNBC, defined as AR greater than 0% on immunohistochemistry staining, derived clinical benefit from enzalutamide therapy in the phase 2 MDV3100-11 study (NCT01889238).17

Results demonstrated that the clinical benefit rate, defined as confirmed complete or partial responses or stable disease, with enzalutamide monotherapy was 33% (95% CI, 23%-45%) at 16 weeks and 28% (95% CI, 19%-39%) at 24 weeks among evaluable patients (n = 78) and 25% (95% CI, 17%-33%) and 20% (95% CI, 14%-29%), respectively, for the intention-to-treat population (N = 118).17

In another study (NCT02750358), Traina and coinvestigators examined the feasibility of 1 year of adjuvant enzalutamide therapy for patients with early-stage AR-positive (≥ 1%) TNBC. Overall, 33 of 47 evaluable patients were able to complete 52 weeks of therapy, according to findings presented at the 2019 American Society of Clinical Oncology Meeting. The 1-year disease-free survival rate was 93.5% (95% CI, 86.6%-100%).18

The early signals have been strong enough to secure funding from the Breast Cancer Research Foundation and support from the Translational Breast Cancer Research Consortium to launch a randomized trial that will test enzalutamide against therapies chosen by individual physicians at multiple locations in the United States, Traina said.

“It’s been exciting to move from that initial observation, that the androgen receptors existed, to multiple phase 1 trials to establish that these prostate cancer drugs are safe in women with breast cancer, to early phase 2 trials and now to a randomized trial,” Traina said.

“If your cancer is very driven by hormones, then actually targeting that pathway instead of using chemotherapy may offer a really well-tolerated approach. The idea is that you could start with an endocrine approach in these androgen-driven triple-negative cancers and, at some point, introduce chemotherapy if necessary, not unlike the way we manage an estrogen-driven cancer with [estrogen receptor]-targeted therapies,” she said.

COVID-19 CASTS A SHADOW
For Traina, specializing in medicine in general and oncology in particular was a natural choice. “I unfortunately had the experience of losing my mother to cancer while I was quite young, and I believe that is what first inspired me to enter into this field,” she said. “I couldn’t imagine doing anything else, to be honest. This is such meaningful work, and it is a privilege to partner with my patients and their families during this experience.

“It is empowering to be able to offer guidance and hope for my patients through their individual journeys,” she added.

“Also, this is a tremendously exciting time in the science of oncology. It’s humbling to be a part of the research that is [affecting] survival for women with breast cancer.”

Traina has spent more than 20 years in the medical field, having obtained her medical degree from Weill Cornell Medicine in 1999. She joined the staff at MSK after participating in a fellowship in medical oncology and hematology at the center. She completed a residency in internal medicine at NewYork-Presbyterian Weill Cornell and served as chief resident and chief fellow at MSK.

As Traina and colleagues continue their search for better therapies, they now face an entirely novel challenge—delivering care safely and effectively amid the COVID-19 pandemic. This year’s CFS® agenda features presentations on the association of inflammation, cancer, and COVID-19 and a panel discussion on experiences with COVID-19 in the oncology arena. Norman E. “Ned” Sharpless, MD, director of the National Cancer Institute, is scheduled to provide the agency’s perspective on COVID-19.

“It’s impossible to ignore the global pandemic and how it’s [affecting] our delivery of care, so it’s one of the major issues that will be addressed at the symposium,” Traina said. “We are all finding innovative ways to continue to deliver high-quality care in a safe environment, one that incorporates social distancing, appropriate PPE [personal protective equipment], psychosocial support, and family safety. Speakers and panelists and, presumably, many participants will be talking about their personal experiences.

“There’s a portion of the agenda that is dedicated to telemedicine and how there’s a digital transformation going on in health care delivery, one that may remain, at least in part, after the pandemic is over,” she added.

The medical field’s understanding of the risk that COVID-19 poses to patients with cancer, including those undergoing active treatment, continues to evolve. Findings from a study of 423 patients with COVID-19 treated at MSK indicate that age older than 65 years and treatment with ICIs were associated with higher rates of hospitalization and severe disease, but chemotherapy and major surgery were not.19 Meanwhile, concern is growing about the future burden of cancer among patients who delay screenings or medical visits that could lead to a diagnosis.

“When the pandemic began, patients were fearful of leaving their homes to receive important cancer care. People also have delayed age-appropriate screening studies, where the risk-benefit balance might have favored avoiding coronavirus and putting off screening and surveillance studies,” Traina said.

“There is a body of literature that suggests we’ll see a wave of cancer diagnoses ahead, perhaps at a later stage, because of the delays in diagnosis that have happened as a result of the pandemic,” she noted.

In addition to necessitating changes in the delivery of cancer care, the pandemic has altered the realm of continuing medical education conferences. PER® quickly adapted its offerings to a live, interactive, virtual format, and Traina anticipates a smooth experience for CFS® attendees.

“Now that we are several months into the COVID-19 pandemic, we have become quite familiar with using virtual platforms to effectively convey meeting content,” she said. “Our presenters will be able to deliver the content as effectively via the internet as they could do in person.”

Indeed, Traina believes that the virtual symposium could improve upon standard conferences in several ways. For example, live chat features will allow all participants to engage in the meeting in a way that might not have been possible in person.

The real challenge involves translating a conference’s social element to the virtual realm. “We are working to create that sense of community and reinvent the social aspect of the meeting,” Traina said. “We are looking for ways to facilitate interactions between participants and leaders in the field. I’m optimistic that we’ll meet that goal.”
Beating the Odds
ONE
PATIENT
at a time

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Adjuvant Osimertinib May Revolutionize NSCLC Care, But Longer Follow-Up Is Needed

by GINA COLUMBUS

RESULTS FROM THE PHASE 3 ADAURA trial (NCT02511106) demonstrated a notable disease-free survival (DFS) benefit observed with the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib (Tagrisso) as an adjuvant treatment in patients with EGFR-mutant non-small cell lung cancer (NSCLC). However, longer follow-up will determine whether the data are sufficient to change practice for the adjuvant setting of NSCLC, specifically for patients with EGFR mutations, said Heather A. Wakelee, MD, in a presentation during the 21st Annual International Lung Cancer Congress®, a program by Physicians’ Education Resource®, LLC (PER®).1

“This is a very striking, early separation of curves; we can argue whether or not that was expected,” said Wakelee, a professor of medicine (oncology) at Stanford University/Stanford Cancer Institute. “I would say ‘yes’—we were fully expecting to see a DFS benefit, based on what we have observed in earlier trials with other EGFR TKIs. When you look at the separation here, [the DFS benefit] is much more striking. In earlier trials, [the hazard ratio (HR)] ranged from 0.5 to 0.6.

Here, we are dealing with an HR of less than 0.2. I don’t think any of us are going to say that this DFS benefit is anything other than statistically significantly different.”

To date, the status of adjuvant treatment for patients with NSCLC has been found to be equivalent to neoadjuvant chemotherapy; both approaches translate to a survival benefit for patients. However, clinical trial findings have been mixed. The use of adjuvant chemotherapy was explored in an analysis conducted by the Lung Adjuvant Cisplatin Evaluation and NSCLC Meta-Analysis Collaborative Group. The analysis, which evaluated 5 trials comprising 4584 patients with NSCLC, showed that this approach led to a modest overall survival (OS) benefit (HR, 0.89; 95% CI, 0.82-0.96; P = .005) and an OS benefit at 5 years of 5%.2 The use of adjuvant chemotherapy was explored in an analysis conducted by the Lung Adjuvant Cisplatin Evaluation and NSCLC Meta-Analysis Collaborative Group. The analysis, which evaluated 5 trials comprising 4584 patients with NSCLC, showed that this approach led to a modest overall survival (OS) benefit (HR, 0.89; 95% CI, 0.82-0.96; P = .005) and an OS benefit at 5 years of 5%.

The OS improvement was more pronounced in patients with stage II/III disease (HR, 0.83; 95% CI, 0.73-0.95) compared with stage IB (HR, 0.93; 95% CI, 0.78-1.10) or stage I A disease (HR, 1.40; 95% CI, 0.95-2.06).

Furthermore, updated individual data of adjuvant chemotherapy in patients treated on or after January 1, 1965, included 34 trials comprising 8447 patients and showed an HR of 0.86 for OS (95% CI, 0.81-0.92; P < .001).3 The absolute benefit at 5 years with this treatment was 4%.

Other adjuvant chemotherapy trials highlighted a modest recurrence-free survival (RFS) benefit achieved with various regimens. For example, in the JIPANG trial, the investigator-assessed median RFS was 37.3 months with vinorelbine/cisplatin versus 38.9 months with pemetrexed/cisplatin at a median follow-up of 45.2 months (HR, 0.98; 95% CI, 0.81-1.20; 1-sided log-rank P = .474; 2-sided log-rank P = .948).4 The 24-month RFS rates were 60.7% and 58.3%, respectively, and the respective 36-month RFS rates were 50.2% and 51.1%.

OS served as a secondary end point of the trial. The median OS was not reached in either arm (HR, 0.98; 95% CI, 0.71-1.35; 1-sided log-rank P = .434; 2-sided log-rank P = .868). Additionally, the 24-month OS rates were 91.8% and 92.5% with vinorelbine/cisplatin and pemetrexed/cisplatin and the 36-month OS rates were 83.5% and 87.2%, respectively.

Erlotinib (Tarceva) was also examined as an adjuvant treatment in patients with resected
stage I to IIIA disease that was either EGFR-positive or amplified by fluorescence in situ hybridization in the RADIANT trial (NCT00373425). Patients were randomized 2:1 to receive erlotinib at 150 mg orally once daily for 2 years or placebo for 2 years. No statistically significant difference in DFS was observed; the median DFS was 50.5 months for erlotinib and 48.2 months for placebo (HR, 0.90; 95% CI, 0.74–1.10; P = .324).3

Among 161 patients (16.5%) in the EGFR-mutant-positive subgroup, DFS favored erlotinib at a median 46.4 months versus 28.5 months (HR, 0.61; 95% CI, 0.38–0.98; P = .039), but this was not determined to be statistically significant due to a hierarchical testing procedure. Also, in the EGFR-mutant-positive group, the median OS was not reached in either arm (HR, 1.09; 95% CI, 0.54–2.16; P = .815). Overall, the HRs for DFS and OS were 0.90 and 1.13, respectively.

Moreover, the ADJUVANT CTONG 1104 trial (NCT01405079), which evaluated adjuvant gefitinib (Iressa) versus vinorelbine plus cisplatin, showed a DFS benefit with the EGFR TKI in patients with stage II to IIIA (N1-N2) disease. Here, the median DFS was 28.7 months with gefitinib and 18.0 months for vinorelbine plus cisplatin (HR, 0.92; 95% CI, 0.42–0.87; P = .005); the 3-year DFS rate was 34% versus 27%.4 However, gefitinib was not found to result in an improvement in OS; the median OS was 62.8 months with gefitinib and vinorelbine/cisplatin, respectively (HR, 0.92; 95% CI, 0.62–1.36; P = .674).

The ADAURA trial, however, has had the most recent readout in this setting. In the international, randomized, placebo-controlled, double-blind, phase 3 study, 682 patients with primary nonsquamous stage IB to IIIA NSCLC harboring EGFR mutations, with exon 19 deletions or L858R mutations, were randomized 1:1 to receive 80 mg of osimertinib once daily or once-daily placebo. Interim results showed that adjuvant treatment with osimertinib led to an 83% reduction in the risk of disease recurrence or death in patients with stage II to IIIA EGFR-mutant NSCLC (HR, 0.17; 95% CI, 0.12–0.23; P < .0001).5 At 33% maturity, the median DFS was not reached (95% CI, 38.8 months to not calculable [NC]) with osimertinib compared with 20.4 months (95% CI, 16.6–24.5) with placebo. Additionally, in patients with stage IB to IIIA disease, which was the overall study population, osimertinib demonstrated a 79% reduction in the risk of disease recurrence or death (HR, 0.21; 95% CI, 0.16–0.28; P < .0001).

When looking at the overall population of patients with stage IB to IIIA disease, the median DFS was also not reached with osimertinib (95% CI, NC to NC) and was 28.1 months (95% CI, 22.1–35.8) with placebo at 29% maturity. In the stage II to IIIA population, the DFS rates at 1, 2, and 3 years were 97%, 90%, and 80% with osimertinib, respectively; these rates were 61%, 44%, and 28%, respectively, with placebo.

In the overall population, osimertinib led to DFS rates at 1, 2, and 3 years of 97%, 89%, and 79%, respectively. In the placebo arm, these rates were 69%, 53%, and 41%, respectively. The DFS benefit with osimertinib was also observed in subgroups across the entire population, regardless of race, stage of disease, and type of EGFR aberration. While OS data are immature, early survival findings showed that the median OS was not reached in both arms, with a 60% reduction in the risk of death (HR, 0.40; 95% CI, 0.18–0.90).

Osimertinib was well tolerated with a safety profile that was consistent with prior findings. The most frequent adverse effects (AEs) included diarrhea, paronychia, and dry skin, although the majority of these were of grade 1/2 in severity. Grade 3/4 AEs were low.

Interstitial lung disease was reported in 3% of patients on osimertinib; additionally, QTc prolongation was reported in 7% of patients in the osimertinib arm versus 1% of patients in the placebo arm.

“We will see how [ADAURA] pans out over time; it’s still too early to make too much of this. However, one has to wonder: Are we going to be in a similar situation to what we have seen in the other trials, where there is a striking DFS benefit that prolongs recurrence, but it does not necessarily translate to an OS benefit?” Wakelee asked. “[This means] that perhaps we are not curing patients, we are just delaying when the disease recurs. The benefit of that then is something to discuss. There clearly is a benefit to delaying recurrence of disease, but it’s different than when we are actually potentially curing patients, as we have been shown to do with chemotherapy—although [it has been in] a small subset.”

Beyond chemotherapy and TKIs, immunotherapy is also being explored in the adjuvant setting of NSCLC in a number of ongoing studies (TABLE).

“We are waiting for the results of these trials; it is unclear when we will have readout, but hopefully we’ll see data fairly soon,” concluded Wakelee.
**INDICATION**

PADCEV (enfortumab vedotin-ejfv) is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

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

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

Hyperglycemia occurred in patients treated with PADCEV, including death and diabetic ketoacidosis (DKA), in those with and without pre-existing diabetes mellitus. The incidence of Grade 3–4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In one clinical trial, 8% of patients developed Grade 3–4 hyperglycemia. Patients with baseline hemoglobin A1C ≥8% were excluded. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Peripheral neuropathy (PN), predominantly sensory, occurred in 49% of the 310 patients treated with PADCEV in clinical trials; 2% experienced Grade 3 reactions. In one clinical trial, peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 was 3.8 months (range: 0.6 to 9.2). Neuropathy led to treatment discontinuation in 6% of patients. At the time of their last evaluation, 15% had complete resolution, and 26% had partial improvement. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy.

Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes. Dry eye symptoms occurred in 36% of patients, and blurred vision occurred in 14% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.9 months (range: 0.3 to 6.2). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Skin reactions occurred in 54% of the 310 patients treated with PADCEV in clinical trials. Twenty-six percent (26%) of patients had maculopapular rash and 30% had pruritus. Grade 3–4 skin reactions occurred in 10% of patients and included symmetrical drug-related intertriginous and flexural exanthema (SDRFE), bullous dermatitis, exfoliative dermatitis, and palmoplantar erythrodysesthesia. In one clinical trial, the median time to onset of severe skin reactions was 0.8 months (range: 0.2 to 5.3). Of the patients who experienced rash, 65% had complete resolution and 22% had partial improvement. Monitor patients for skin reactions. Consider appropriate treatment, such as topical corticosteroids and antihistamines for skin reactions, as clinically indicated. For severe (Grade 3) skin reactions, withhold PADCEV until improvement or resolution and administer appropriate medical treatment. Permanently discontinue PADCEV in patients that develop Grade 4 or recurrent Grade 3 skin reactions.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 310 patients, 1.3% of patients experienced skin and soft tissue reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2–7 days after extravasation and resolved within 1–4 weeks of peak. One percent (1%) of patients developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-fetal toxicity PADCEV can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose. Advise male patients...
with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS
Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, and sepsis (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). Adverse reactions leading to dose interruption occurred in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).

The most common adverse reactions (≥20%) were fatigue (56%), peripheral neuropathy (56%), decreased appetite (52%), rash (52%), alopecia (50%), nausea (45%), dysgeusia (42%), diarrhea (42%), dry eye (40%), pruritus (26%) and dry skin (26%). The most common Grade ≥3 adverse reactions (≥5%) were rash (13%), diarrhea (6%) and fatigue (6%).

LAB ABNORMALITIES
In one clinical trial, Grade 3-4 laboratory abnormalities reported in ≥5% were: lymphocytes decreased (10%), hemoglobin decreased (10%), phosphate decreased (10%), lipase increased (9%), sodium decreased (8%), glucose increased (8%), urate increased (7%), neutrophils decreased (5%).

DRUG INTERACTIONS
Effects of other drugs on PADCEV Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with strong CYP3A4 inhibitors.

12% CR (n=15/125)
32% PR (n=40/125)
7.6-month median DOR
(95% CI: 6.3, NE; range: 0.95, 11.3+ months; 10.2 months median follow-up)

• PADCEV™ is an antibody-drug conjugate that requires no biomarker testing.

*The EV-201 trial was a single-arm, multicenter trial of 125 patients with locally advanced or metastatic urothelial cancer who had previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Patients received 1.25 mg/kg of PADCEV via IV infusion over 30 minutes on days 1, 8, and 15 of every 28-day cycle and continued to receive treatment until disease progression or unacceptable toxicity.

The efficacy outcome measures, confirmed ORR and DOR, were assessed by BICR using RECIST v1.1. ORR consisted of confirmed CR and PR. CR was defined as the disappearance of all target lesions. PR was defined as a ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Median duration of follow-up was 10.2 months.

SPECIFIC POPULATIONS
Lactation Advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Hepatic impairment Avoid the use of PADCEV in patients with moderate or severe hepatic impairment.

Please see Brief Summary of full Prescribing Information on adjacent page.

BICR=blinded independent central review; CI=confidence interval; CR=complete response; DOR=duration of response; FDA=US Food and Drug Administration; IV=intravenous; NE=not estimable; ORR=objective response rate; PD-1=programmed death receptor-1; PD-L1=programmed death-ligand 1; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.


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PADCEV™ (enfortumab vedotin-ejfv) for injection, for intravenous use

The following is a brief summary of full Prescribing Information. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE
PADCEV is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

This indication is approved under accelerated approval based on tumor shrinkage rate from the phase 1b/2a EV-201 study. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modifications

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>Dose Modification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Blood glucose &gt;250 mg/dL</td>
<td>Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.</td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Grade 2</td>
<td>Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or recurrent Grade 3</td>
<td>Permanently discontinue.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Reactions</td>
<td>Grade 3 (severe)</td>
<td>Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.</td>
<td></td>
</tr>
<tr>
<td>Grade 4 or recurrent Grade 3</td>
<td>Permanently discontinue.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other nonhematologic toxicity</td>
<td>Grade 3</td>
<td>Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>Grade 3, or Grade 2 thrombocytopenia</td>
<td>Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

WARNINGS AND PRECAUTIONS

Hyperglycemia

Hyperglycemia occurred in patients treated with PADCEV, including death, and diabetic ketoacidosis (DKA) in those with and without pre-existing diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In EV-201, 8% of patients developed Grade 3-4 hyperglycemia. In this trial, patients with baseline hemoglobin A1C ≥8% were excluded. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated >250 mg/dL, withhold PADCEV.

Peripheral neuropathy (PN)

Peripheral neuropathy, predominantly sensory, occurred in 49% of the 310 patients treated with PADCEV in clinical trials; 2% experienced Grade 3 reactions. In study EV-201, peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 was 3.8 months (range: 0.6 to 9.2). Neuropathy led to treatment discontinuation in 6% of patients. At the time of their last evaluation, 19% had completed resolution, and 26% had partial improvement. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy.

Ocular disorders

Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes. Dry eye symptoms occurred in 38% of patients, and blurred vision occurred in 14% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.9 months (range: 0.3 to 6.2). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Skin Reactions

Skin reactions occurred in 54% of the 310 patients treated with PADCEV in clinical trials. Twenty-six percent (26%) of patients had maculopapular rash and 36% had pruritus. Grade 3-4 skin reactions occurred in 10% of patients and included symmetrical drug-related interstitial and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmoplantar erythrodysesthesia. In study EV-201, the median time to onset of severe skin reactions was 0.8 months (range: 0.2 to 34 months). Of the 310 patients who experienced rash, 65% had complete resolution and 22% had partial improvement. Monitor patients for skin reactions. Consider appropriate treatment, such as topical corticosteroids and antihistamines for skin reactions, as clinically indicated. For severe (Grade 3) skin reactions, withhold PADCEV until improvement or resolution and administer appropriate medical treatment. Permanently discontinue PADCEV in patients that develop Grade 4 or recurrent Grade 3 skin reactions.

Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 310 patients, 1.3% of patients experienced skin and soft tissue reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. One percent of patients developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the clinical exposures at the recommended human dose of 1.25 mg/kg. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose of PADCEV. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Clinical Trial Experience

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

The data in the WARNINGS AND PRECAUTIONS section reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 310 patients in EV-201, EV-101 (NCT02091999), and EV-102 (NCT03219333). Among 310 patients receiving PADCEV, 30% were exposed for ≥ 6 months and 8% were exposed for ≥12 months.

The data described in this section reflect exposure to PADCEV from EV-201, a single arm study in patients (N=125) with locally advanced or metastatic urothelial cancer who had received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. Patients received PADCEV 1.25 mg/kg on Days 1, 8, and 15 for 28 days as single agent until disease progression, unacceptable toxicity or grade 3/4 toxicities. The median duration of exposure to PADCEV was 4.6 months (range: 0.5-15.8 months).

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (8%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, and sepsis (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (8%). Adverse reactions leading to dose interruption occurred
Effects of Other Drugs on PADCEV

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or other enfortumab vedotin-ejfv products may be misleading. A total of 365 patients were tested for immunogenicity to PADCEV; 4 patients (1%) were confirmed to be transiently positive for anti-therapeutic antibody (ATA), and 1 patient (0.3%) was confirmed to be persistently positive for ATA at any post-baseline time point. No impact of ATA on efficacy, safety and pharmacokinetics was observed.

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

Stated in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%). The most common adverse reactions (≥20%) were fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin. The most common Grade ≥3 adverse reaction (≥5%) were rash, diarrhea, and fatigue.

Table 1 summarizes the all grade and Grade ≥3 adverse reactions reported in patients in EV-201.

Table 1. Adverse Reactions Reported in ≥15% (Any Grade) or ≥5% (Grade ≥3) of Patients Treated with PADCEV in EV-201

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PADCEV All Grades</th>
<th>PADCEV Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>100%</td>
<td>73%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy†</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>52</td>
<td>13</td>
</tr>
<tr>
<td>Alopecia</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus§</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye¶</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes: asthenia and fatigue
†Includes: hypesthesia, gait disturbance, muscular weakness, neuralgia, paresthesia, peripheral motor neuroopathy, peripheral sensory neuroopathy and peripheral sensorimotor neuroopathy.
§Includes: dermatitis acrocinem, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, skin exfoliation, stasis dermatitis, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and urticaria.
¶Includes: pruritus and pruritus generalized
§§Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased.
*Includes: colitis, diarrhea and enterocolitis

Other clinically significant adverse reactions (≥15%) include: herpes zoster (3%) and infusion site extravasation (2%).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or other enfortumab vedotin-ejfv products may be misleading. A total of 365 patients were tested for immunogenicity to PADCEV; 4 patients (1%) were confirmed to be transiently positive for anti-therapeutic antibody (ATA), and 1 patient (0.3%) was confirmed to be persistently positive for ATA at any post-baseline time point. No impact of ATA on efficacy, safety and pharmacokinetics was observed.

Strong CYP3A4 Inhibitors

Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the exposures at the recommended human dose of 1.25 mg/kg. Advise patients of the potential risk to the fetus.

Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Males

Based on findings from animal studies, PADCEV may impair male fertility.

Pediatric Use

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

Geriatric Use

Of the 310 patients treated with PADCEV in clinical studies, 187 (60%) were 65 years or older and 80 (26%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment. PADCEV has not been studied in patients with moderate or severe hepatic impairment. In another ADC that contains MMAE, the frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment.

Renal Impairment

No dose adjustment is required in patients with mild (CrCl >60-90 mL/min), moderate (CrCl 30-60 mL/min) or severe (CrCl <30 mL/min) renal impairment.

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81-0293-PM
Investigator Sees Potential for Earlier TKI Use in EGFR+ Tumors

by DENISE MYSHKO

THE INTRODUCTION OF TYROSINE kinase inhibitor (TKI) therapy earlier in the treatment timeline for patients with EGFR-mutant non-small cell lung cancer (NSCLC) holds the promise of improving overall survival (OS) for this patient population, according to Frances A. Shepherd, MD.

EGFR TKIs have delivered improvements in progression-free survival (PFS) over chemotherapy as first-line therapy for patients with the mutation in clinical trials in advanced and metastatic disease settings, but investigators have been looking for ways to boost OS results, Shepherd said during a presentation at the virtual 21st Annual International Lung Cancer Congress.1

Now the recently reported findings from the phase 3 ADAURA trial (NCT02511106) demonstrate a role for osimertinib (Tagrisso), a third-generation EGFR TKI, as adjuvant therapy in patients with early-stage disease, Shepherd noted.2

“We’ve gone from nihilism to hope in the [past] 15 years,” said Shepherd, a 2016 Giants of Cancer Care award winner who is the Scott Taylor Chair in Lung Cancer Research at Princess Margaret Cancer Centre in Toronto, Canada. “[I’m hoping] that finally we will be able to introduce EGFR TKI therapy at a time when we can change the cure rate and not just the PFS.”

Shepherd, who also is a professor at the University of Toronto, said EGFR TKIs are “never curative in advanced EGFR-mutant NSCLC.” She said several studies that tested the first-generation EGFR TKIs erlotinib (Tarceva) or gefitinib (Iressa) in the adjuvant setting demonstrated a hazard ratio benefit for disease-free survival (DFS) versus placebo or chemotherapy but not an OS benefit.

At the same time, she noted, adjuvant chemotherapy for patients with EGFR-mutant NSCLC resulted in improvements in DFS (HR, 0.58) and OS (HR, 0.44) in the JBR.10 trial (NCT00002583).1 In that study, patients with completely resected stage II or stage IIIA NSCLC were randomized to receive cisplatin plus vinorelbine or observation.3

“Do not forget there is an enormous survival benefit from chemotherapy because these patients respond so well,” Shepherd said.

ADAURA RESULTS OPEN DOOR FOR ADJUVANT EGFR TKIs

In ADAURA, investigators randomized 682 patients to receive either osimertinib at 80 mg once daily or placebo, with treatment continuing for 3 years until disease recurrence, completion, or discontinuation criteria are met. The study population consisted of patients with completely resected stage IB, II, or IIIA NSCLC with or without adjuvant chemotherapy after surgery.

In patients with stage II to IIIA disease, osimertinib therapy reduced the risk of disease recurrence or death by 83% (HR, 0.17; 95% CI, 0.12-0.23; P < .0001). The median DFS in months was not reached with osimertinib (95% CI, 38.8-not calculable [NC]) compared with 20.4 months (95% CI, 16.6-24.5) with placebo. In the overall trial population, a key secondary end point, osimertinib demonstrated a reduction in the risk of disease recurrence or death of 79% (HR, 0.21; 95% CI, 0.16-0.28; P < .0001). The median DFS was not reached with osimertinib (95% CI, NC-NC) versus 28.1 months with placebo (95% CI, 0.16-0.28).2

The 2-year DFS rates with osimertinib were 87% for patients with stage IB disease, 91% for stage II, and 88% for stage IIIA compared with 73%, 56%, and 32%, respectively, for placebo.

The ADAURA study was unblinded early upon recommendation of an independent monitoring committee. At the time of the unblinding, the study had completed enrollment and all patients had been followed up for at least 1 year. Shepherd said the panel looked at “these enormous differences in disease-free survival. We never saw anything like this with chemotherapy.”

Shepherd said there was no subset that did not derive benefit from adjuvant osimertinib. OS findings were immature at data cutoff (3% maturity for osimertinib, 7% for placebo). Median OS was not reached with either osimertinib or placebo, but the trend showed a benefit with osimertinib (HR, 0.40; 95% CI, 0.18-0.90).2 “They gave us an early snapshot of overall survival,” Shepherd said, adding that, “It is too early to tell,” but the osimertinib curve appears to be on top.

Osimertinib is very well tolerated, Shepherd said. “There were very few grade 3 or 4 toxicities. The pneumonitis that we fear from early reports from Asia was minimal and the same in both arms, and the QTc prolongation was seen in 22 patients and 4 in the placebo group. Those important toxicities were present but not at an unexpected level or a level that would cause us to worry in the curative situation.”

The ADAURA study is continuing to assess OS as a secondary endpoint. Moving forward, Shepherd said, investigators would need to evaluate more data including patterns of recurrence, particularly for central nervous system (CNS) relapse. “We know that osimertinib has great CNS penetration,” Shepherd said.

Osimertinib initially was approved by the FDA in November 2015 for treating patients with metastatic NSCLC whose tumors harbor the EGFR 1790M mutation and who have progressed on or after EGFR TKI therapy. The drug was approved in the first-line setting for patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations after demonstrating significantly improved PFS and overall response rates over gefitinib or erlotinib therapy in the FLAURA trial (NCT02296125).4

For a full list of references, see the article at https://bit.ly/3b280L6.
Lara Shares Immunotherapy Updates for Extensive-Stage Small Cell Lung Cancer

by HAYLEY VIRGIL

ALTHOUGH PLATINUM-BASED chemotherapy given concurrently with a PD-L1 inhibitor has become the standard of care for the frontline treatment of patients with extensive-stage small cell lung cancer (ES-SCLC), investigators have found that maintenance immunotherapy and combination strategies have fallen short of expectations, according Primo N. Lara Jr, MD.1

“Platinum-based chemotherapy concurrent with a PD-L1 inhibitor, either atezolizumab (Tecentriq) or durvalumab (Imfinzi), is the frontline standard of care. Maintenance immunotherapy and combination immune checkpoint inhibitors, such as durvalumab and tremelimumab, have missed the mark,” said Lara, the executive associate dean for cancer programs, School of Medicine, at the University of California (UC) Davis Comprehensive Cancer Center.

“In the second-line or beyond setting, pembrolizumab (Keytruda) and nivolumab (Opdivo) [have been] approved. As we always say, if you have a patient who is in fair shape, send [them] to us for a clinical trial,” he said.

During the 21st Annual International Lung Cancer Congress®, a program developed by Physicians’ Education Resource®, LLC (PER®), Lara, who also holds the Codman-Radke Endowed Chair in Cancer Research and is a professor and the director of the UC Davis Comprehensive Cancer Center, highlighted the latest advances made with immunotherapy in SCLC, research done in the maintenance setting, and approaches for the second-line setting and beyond.

IMPOWER133

The standard of care for patients with ES-SCLC is platinum-based chemotherapy plus a PD-L1 inhibitor, and this approach was examined in the IMpower133 study (NCT02763579). Specifically, in the pivotal phase 3 trial, investigators examined the efficacy of atezolizumab in combination with carboplatin and etoposide.2 The trial enrolled 500 patients with histologically documented ES-SCLC who had not received prior treatment for their disease and had an ECOG performance score of 0 or 1. Patients with an autoimmune disease or who had active central nervous system (CNS) metastases were excluded from the trial. Patients were randomized 1:1 to receive either atezolizumab, carboplatin, and etoposide, or carboplatin, etoposide, and placebo. The coprimary end points of the trial were overall survival (OS) and progression-free survival (PFS).

Results showed a notable median OS benefit for patients on the atezolizumab arm, with an HR of 0.70, translating to a 30% reduction in risk of death. Patients on this arm also experienced a more favorable median PFS (HR, 0.77). Most of the patient subgroups analyzed in the trial benefited from atezolizumab, according to Lara.

The addition of atezolizumab to chemotherapy did not result in a significant increase in response. The overall response rate (ORR) was 64.4% in the placebo arm compared with 60.2% in the atezolizumab arm. However, those in the atezolizumab arm did experience a higher complete response rate versus those on the placebo arm, at 2.5% versus 1.0%, respectively, noted Lara.

Updated results from an exploratory analysis presented during the 2020 American Association for Cancer Research Virtual Annual Meeting II showed that the combination of atezolizumab plus carboplatin/etoposide continued to demonstrate an improvement in OS versus chemotherapy alone in the frontline treatment of this patient population, regardless of PD-L1 expression and blood tumor mutational burden.3

CASPIAN

In the global, randomized, multicenter phase 3 CASPIAN study (NCT03043872), investigators examined the addition of durvalumab to tremelimumab and etoposide (n = 268) versus either durvalumab plus etoposide (n = 268) or etoposide alone (n = 269) in a total of 805 treatment-naïve patients with World Health Organization performance status of 0 or 1, a life expectancy of 12 weeks or more, and measurable disease per RECIST v1.1 criteria.4 Notably, patients with asymptomatic or treated and stable brain metastases were permitted.

Earlier findings from the trial showed that the addition of durvalumab to chemotherapy reduced the risk of death by 27% versus chemotherapy alone (HR, 0.73; 95% CI, 0.59-0.91; P = .0047). The median PFS was similar between the arms, at 5.1 months with durvalumab versus 5.4 months without (HR, 0.78; 95% CI, 0.65-0.94); however, an analysis of the 12-month PFS rate indicated a large advantage that favored durvalumab, at 17.5% versus 4.7%.

Updated findings presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program showed that the addition of durvalumab to chemotherapy continued to show an improvement in OS in this patient population. Specifically, at a median follow-up of 25.1 months, the median OS was 12.9 months in patients who received the combination therapy compared with 10.5 months in those who only received chemotherapy (HR, 0.75; 95% CI, 0.62-0.91; P = .0032).5

The combination was also found to have a probability of median OS rate of 52.8% at the 12-month mark compared with 39.3% in the chemotherapy-only cohort. The rates were 32.0% versus 24.8% at 18 months and 22.2% versus 14.4% at the 24-month mark, respectively. The updated median PFS rate was 17.9% at 12 months, 13.9% at 18 months, and 11.0% at 24 months with durvalumab plus chemotherapy compared with 5.3% at 12 months, 3.4% at 18 months, and 2.9% at
“Remarkably, at 2 years, nearly one-fourth of the patients [treated with durvalumab and chemotherapy] were still alive. This is a significant achievement.”

—PRIMO N. LARA JR, MD

24 months with chemotherapy alone. Nearly all patient subsets were found to benefit from the durvalumab plus etoposide combination.

“Remarkably, at 2 years, nearly one-fourth of the patients were still alive,” noted Lara. “This is a significant achievement.”

Notably, the addition of tremelimumab to durvalumab plus chemotherapy did not significantly improve outcomes in this patient population. The median PFS was 4.9 months with the triplet versus 5.4 months with chemotherapy alone (HR, 0.84; 95% CI, 0.70-1.01), and the confirmed ORR was 58.4% versus 58.0%, respectively.

Despite safety data revealing that the combination regimen had a higher rate of toxicities—98.1% with durvalumab plus chemotherapy and 97.0% with chemotherapy alone—investigators noted that the safety findings were consistent with the known safety profile of all agents. The results further supported durvalumab plus chemotherapy as a standard of care for patients with ES-SCLC.

KEYNOTE-604

In the phase 3 KEYNOTE-604 trial (NCT03066778), investigators examined the use of pembrolizumab in combination with etoposide and carboplatin (n = 228) versus placebo plus etoposide and carboplatin (n = 225). To be eligible for enrollment, patients had to have stage IV SCLC; have an ECOG performance score of 0 or 1, no unstable brain metastases, adequate organ function, and a life expectancy of 3 months or more.

Results showed an ORR of 70.6% in the pembrolizumab arm versus 61.8% in the placebo arm. The pembrolizumab combination resulted in a statistically significant improvement in PFS compared with chemotherapy (HR, 0.75; 95% CI, 0.61-0.91). Although the combination led to an improvement in OS, it did not meet statistical significance per the prespecified plan (HR, 0.80; 95% CI, 0.64-0.98). The OS rates with the pembrolizumab combination were 45.1% at 12 months and 22.5% at 24 months versus 39.6% and 11.2%, respectively, with the placebo.

“The trial] showed improved PFS and a benefit from pembrolizumab, but it was not enough to make this combination a new standard of care,” Lara said.

CHECKMATE-451

Shifting to the maintenance setting, investigators in the CheckMate-451 trial (NCT02538666) examined the use of single-agent nivolumab maintenance therapy versus the combination of nivolumab plus ipilimumab (Yervoy) in patients with ES-SCLC who had stable disease following first-line platinum-based therapy, an ECOG performance status of 0 to 1, no untreated CNS metastases, and no autoimmune disease. The trial enrolled 810 patients who were randomized 1:1:1 to receive either nivolumab monotherapy, nivolumab plus ipilimumab, or placebo. Results showed that the OS was not significantly prolonged with nivolumab/ipilimumab versus placebo (HR, 0.92; 95% CI, 0.75-1.12; P = .3693) nor was OS improved with nivolumab monotherapy versus the control (HR, 0.84; 95% CI, 0.69-1.02).

“This was a negative trial, whether you’re looking at nivolumab/ipilimumab or nivolumab [alone]. These experimental arms failed to improve outcomes versus placebo, which is very disappointing,” noted Lara.

CHECKMATE-331

In the CheckMate-331 trial (NCT02481830), investigators compared nivolumab monotherapy with either topotecan or amrubicin in the second-line setting. To be eligible for enrollment, patients had to have received 1 prior line of systemic platinum-based therapy or chemoradiation; had to have an ECOG performance status of 0 to 1 and no CNS metastases; and have not received prior treatment with immunotherapy. The trial enrolled a total of 480 patients who were randomized 1:1:1 into the 2 treatment arms. The primary end point of the trial was OS, and secondary end points included ORR and PFS. Results showed that single-agent nivolumab did not improve OS compared with standard topotecan or amrubicin (HR, 0.86; 95% CI, 0.72-1.04).

The trial enrolled a total of 480 patients who were randomized 1:1 into the 2 treatment arms. The primary end point of the trial was OS, and secondary end points included ORR and PFS. Results showed that single-agent nivolumab did not improve OS compared with standard topotecan or amrubicin (HR, 0.86; 95% CI, 0.72-1.04). However, OS curves showed delayed separation after month 12. The median PFS on the investigational arm was 1.4 months versus 3.8 months on the control arm (HR, 1.41; 95% CI, 1.18-1.69).

“[CheckMate-331] was also negative [much like CheckMate-451],” Lara said. “The hazard ratio [was] 0.86 for OS. The PFS favored chemotherapy with a hazard ratio of 1.41.”

KEYNOTE-158

Lastly, KEYNOTE-158 (NCT02628067), which in part led to the recent FDA approval of pembrolizumab for patients with unresectable or metastatic solid tumors that are tumor mutational burden–high, examined the efficacy of pembrolizumab in patients with unresectable or metastatic SCLC who have progressed on or are intolerant to standard therapy; have an ECOG performance score of 0 or 1, and 1 or more measurable lesions; and have no autoimmune disease or noninfectious pneumonitis.

A total of 107 patients were enrolled on the trial. Results showed an ORR of 35.7% in PD-L1-positive patients and 6.0% in PD-L1-negative patients. Moreover, an OS of 53.1% was reported in PD-L1-positive patients at 12 months versus 30.7% in PD-L1-negative patients. Patients who had PD-L1-positive disease also had a higher median OS of 14.9 months compared with 5.9 months in patients with PD-L1-negative disease.

For a full list of references, see the article at https://bit.ly/2OyBGWF.
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Pemigatinib Trial Seeks to Build on Targeted Advances in Cholangiocarcinoma

by DENISE MYSHKO

UNTIL RECENTLY, THERE WERE no molecularly targeted therapies for patients with cholangiocarcinoma. As a result of an explosion of research in the field, the first such targeted therapy, pemigatinib (Pemazyre), was approved in April 2020 for patients with unresectable, previously treated advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement.1,2

Now pemigatinib is being studied in a phase 3 trial to determine whether it can be used as a first-line treatment for this patient population. The FIGHT-302 study (NCT03656536) aims to assess the efficacy and safety of pemigatinib compared with the combination of gemcitabine and cisplatin (FIGURE).3

“Pemigatinib shows significant activity in a group of patients who don’t typically have much of a treatment option. There are data that suggest it may have even a further effect if you give it to untreated patients,” Tanios S. Bekaii-Saab, MD, said in an interview with OncologyLive®. A leading investigator into the drug, Bekaii-Saab is a professor at Mayo Clinic College of medicine and science, the Gastrointestinal Cancer Program leader at Mayo Clinic Cancer Center, and medical director for clinical cancer research at Mayo Clinic in Phoenix, Arizona.

As it stands now, surgery is the only curative treatment for the rare biliary tract cancer but that is an option only for about 35% of patients, and of those who do opt for resection, about 35% relapse within 2 years.4 For patients with unresectable biliary tract cancer, the standard of care is combination therapy with gemcitabine plus cisplatin, based on findings from the phase 3 advanced biliary cancer study ABC-02 (NCT00262769), Bekaii-Saab and colleagues note in a recent article in Future Oncology.5

However, investigators said, survival associated with the combination compared with gemcitabine alone is “significant but modest,” with a median overall survival (OS) of 11.7 months versus 8.1 months (HR, 0.64; 95% CI, 0.52-0.80; P < .001). Although studies continue to assess the gemcitabine/cisplatin combination along with other chemotherapies, investigators say there is an unmet need for better first-line treatments, and targeted approaches have the potential to improve prognosis for patients.5

FIGHT-302 seeks to enroll 432 patients with previously untreated unresectable or stage IV cholangiocarcinoma with FGFR2 rearrangements in 154 locations in the United States, Europe, and Japan. Participants will be randomized 1:1 to receive pemigatinib orally at 13.5 mg daily administered continuously on a 3-week cycle or gemcitabine at 1000 mg/m² plus cisplatin at 25 mg/m² given intravenously on days 1 and 8 of a 3-week cycle for up to 8 cycles. Patients whose disease progresses on the gemcitabine/cisplatin combination will be eligible to cross over to the pemigatinib arm.3,5

The study schema is consistent with evidence about the efficacy of pemigatinib to date, according to Bekaii-Saab. “We have seen significant advantages in the refractory setting; this subgroup of patients with FGFR2 fusion does not seem to respond well to chemotherapy. The crossover design also makes sense because

FIGURE. Pemigatinib Versus Chemotherapy in Cholangiocarcinoma³

Phase 3 FIGHT-302 Trial

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
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<tbody>
<tr>
<td>• Histologically or cytologically confirmed unresectable and/or metastatic cholangiocarcinoma</td>
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<tr>
<td>• No prior systemic treatment</td>
</tr>
<tr>
<td>• Documented FGFR2 rearrangement</td>
</tr>
<tr>
<td>• Evaluable disease by CT or MRI</td>
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<tr>
<td>• ECOG status 0 to 1</td>
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N = 432

Experimental Pemigatinib

Active comparator Gemcitabine + cisplatin

CR, complete response; DCR, disease control rate; DOR, duration of response; FGFR2, fibroblast growth factor receptor 2; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QOL, quality of life; SD, stable disease; TEAE, treatment-emergent adverse effects.
this agent is now approved for second-line treatment,” he said.

RESULTS FROM EARLY STUDIES
Pemigatinib is small-molecule inhibitor of FGFR1/2/3 that, in preclinical studies, has demonstrated activity against cancer cells with FGFR alterations. Overall, FGFR1/2/3 fusions and amplifications have been observed in 11% to 13% of patients with intrahepatic cholangiocarcinoma. The alterations have not been detected in extrahepatic disease.3

The FDA granted an accelerated approval for pemigatinib based on the results of FIGHT-202 (NCT02924376), a multicenter, open-label, single-arm phase 2 study that evaluated patients with locally advanced unresectable or metastatic cholangiocarcinoma who had been treated with at least 1 prior therapy.2

The agency also approved FoundationOne CDx as a companion diagnostic for pemigatinib. The assay is a next-generation sequencing device that detects alterations in 324 genes using DNA isolated from formalin-fixed paraffin-embedded tumor tissue specimens, including FGFR2 fusions and select rearrangements.4 Bekaii-Saab suggests that other commercially available next-generation tests, specifically those that include RNA analysis, may be preferred since they better capture the presence of FGFR2 fusions.

In FIGHT-202, pemigatinib monotherapy demonstrated an overall response rate of 36% (95% CI, 27%-45%), including 2.8% complete and 33% partial response rates, respectively. The median duration of response was 9.1 months (95% CI, 6.0-14.5); 63% of patients achieved a response for 6 months or more and 18% maintained a response for 12 months or more.2 Of note, all responses were observed among those with FGFR2 fusions or rearrangements (n=107); none were evident in study participants with other FGFR2 genetic alterations (n=20) or without FGFR2 genetic alterations (n=18).4

Although OS data were immature at the time of data cutoff, pemigatinib demonstrated median OS of 21.1 months (95% CI, 14.8-not estimable), according to results reported in Lancet Oncology.4

“Overall, these are very impressive results for a group of patients that typically does not do well at all. If we think about second, third, plus lines of treatment in cholangiocarcinoma, the historical average survival published in 1 study is less than 6 to 7 months. In this pretreated subgroup with FGFR2 fusions, we are talking about 21 months,” Bekaii-Saab said.

The antitumor activity of pemigatinib in patients with FGFR2 fusions in FIGHT-202 compares favorably with other second-line chemotherapy and targeted therapies, investigators said. However, they were cautious about comparing pemigatinib with other treatment regimens for cholangiocarcinoma because the study enrolled molecularly selected patients, most of whom (98% in the FGFR2-positive group) had intrahepatic cholangiocarcinoma whereas other studies included patients with all biliary tract cancers without molecular profiling.4

In the FIGHT-202 safety population (N=146), serious adverse effects (AEs) were observed in 45% of patients, with fatal AEs occurring in 4.1% including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion. Nine percent of patients discontinued treatment due to AEs, with causes including intestinal obstruction and acute kidney injury. Dose reduction due to an AE was required in 14% of patients.2

Overall, investigators said the safety profile of pemigatinib was “manageable.” Most AEs were of grade 1 or 2 severity, and these events most commonly included hyperphosphatemia (55%), alopecia (46%), dysgeusia (38%), diarrhea (34%), and fatigue (31%).4

RESEARCH CONTINUES WITH FIGHT-302
FIGHT-302 represents “the largest study with an FGFR2 inhibitor in intrahepatic cholangiocarcinoma specifically for FGFR2 fusions,” Bekaii-Saab said. “This is the first-in-class drug that is approved by the FDA for clinical use. The approval is an accelerated approval pending results of phase 3 studies.”

The primary end point is progression-free survival according to RECIST v1.1 criteria as assessed by independent central review. Secondary outcomes include overall response, OS, duration of response, and quality-of-life assessments.

The study is open label because blinding would have been challenging, Bekaii-Saab said. Pemigatinib is an oral therapy whereas both gemcitabine and cisplatin are administered intravenously. “The toxicities also are a bit different,” he said.

Although cholangiocarcinoma accounts for only 3% of all gastrointestinal malignancies, Bekaii-Saab said there is a significant level of interest in studying targeted strategies and immune therapies.

“Cholangiocarcinoma is a very target-rich disease,” he noted.

Molecular-profiling technologies have identified potentially actionable genetic mutations that may be present in about 40% of patients with cholangiocarcinoma. Frequently altered genes in intrahepatic cholangiocarcinoma include TP53, KRAS, IDH1/2, and CDKN2A/B.

Pemigatinib is being developed by Incyte, a biopharmaceutical company based in Wilmington, Delaware.

REFERENCES
Rini Reviews Key ASCO 2020 Highlights in Genitourinary Cancers

by CAROLINE SEYMOUR

EFFICACY RESULTS FOR APPROACHES in bladder cancer, first-line treatment advances in renal cell carcinoma (RCC), and the effect of prostate-specific membrane antigen (PSMA)-based imaging techniques in nonmetastatic prostate cancer were all part of the key updated data presented across the treatment landscape for genitourinary cancers during the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program.

As part of the 2020 ASCO Direct Highlights® webcast, a program developed by Physicians’ Education Resource®, LLC (PER®), Brian I. Rini, MD, chief of clinical trials at Vanderbilt-Ingram Cancer Center and professor of medicine in the Division of Hematology/Oncology at Vanderbilt University Medical Center in Nashville, Tennessee, provided insight on key developments in genitourinary cancers.

MAINTENANCE AND ADJUVANT APPROACHES IN BLADDER CANCER

The phase 3 JAVELIN Bladder 100 trial (NCT02603432) compared the efficacy of maintenance avelumab (Bavencio) in combination with best supportive care (BSC; n = 350) versus BSC alone (n = 350) in 700 patients with unresectable locally advanced or metastatic urothelial carcinoma whose disease did not progress on 4 to 6 cycles of standard gemcitabine plus cisplatin or carboplatin.

The trial met its primary end point by demonstrating a significant improvement in overall survival (OS) with frontline avelumab maintenance in both the overall and PD-L1-positive populations. Results presented during the meeting showed that those who received avelumab plus BSC had an OS of 71% at 12 months and 61% at 18 months compared with 58% and 44%, respectively, in those who received BSC. The median OS was 21.4 months versus 14.3 months with BSC alone (HR, 0.69; 95% CI, 0.56-0.86; P < .001).

The OS was also longer with the addition of avelumab across all prespecified subgroups. "[This is] a very notable improvement, and [it could be] the first time that a median survival above 20 months—even above 16 or 18 months—has ever been recorded in bladder cancer," Rini said. "These data are striking and standard-of-care-changing results."

Investigators also saw an improvement in median progression-free survival (PFS) with the addition of the PD-L1 inhibitor. Specifically, the median PFS via independent radiology review in the overall population was 3.7 months in the avelumab arm versus 2 months in the BSC arm (HR, 0.62; 95% CI, 0.52-0.75; P < .001).

The bladder cancer community was pleasantly surprised by these results," Rini said. "Some of the other [efforts to combine] chemotherapy with immunotherapy [in this space],...have not been as strikingly positive. The integration of immuno-oncology in bladder cancer is ever evolving, and it’s going to be trickier than it has been for other diseases."

Data from this trial led to the June 2020 FDA approval of avelumab for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-based chemotherapy.

Less positive were the results reported from the phase 3 IMvigor010 study (NCT02450331), which evaluated adjuvant atezolizumab (Tecentriq) versus observation in high-risk muscle-invasive urothelial carcinoma (MIUC). To be eligible for enrollment, patients with high-risk MIUC needed to have undergone radical cystectomy or nephroureterectomy with lymph node dissection within 14 weeks. Participants were randomized 1:1 to receive either 16 cycles of atezolizumab at 1200 mg every 3 weeks or observation only.

The trial did not meet its primary end point of disease-free survival (DFS) with the agent in the general population or in the prespecified subgroups. Within the intent-to-treat (ITT) population, a median DFS of 19.4 months was reported in the atezolizumab arm versus 16.6 months in the observation arm. The 18-month DFS rate was 51% in the atezolizumab arm versus 49% in the observation-only arm (HR, 0.89; 95% CI, 0.74-1.08; P = .02446).

Although atezolizumab showcased a safety profile consistent with what was observed in previous studies in the advanced setting, higher frequencies of grade 1 or 2 adverse events of special interest were reported, along with treatment discontinuation because of toxicities.

"The approach] was certainly safe, but [the trial] did not meet its primary end point of DFS, either in the ITT or prespecified subgroups," Rini said. "The OS follow-up is ongoing and other trials are examining other agents in this setting. However, [these are] somewhat disappointing initial result[s] as the first study to explore adjuvant immunotherapy in high-risk bladder cancer."

FIRST-LINE COMBINATION THERAPY IN RENAL CELL CARCINOMA

Rini also discussed updated data from the phase 3 KEYNOTE-426 trial (NCT02853331), which showed that pembrolizumab (Keytruda) combined with axitinib (Inlyta) continued to demonstrate a clinically significant improvement in efficacy compared with standard-of-care sunitinib (Sutent) in untreated, advanced RCC.

Patients considered for KEYNOTE-426 had newly diagnosed or recurrent stage IV clear cell RCC, had received no prior systemic treatment for advanced disease, and had measurable disease per RECIST v1.1 criteria. A total of 861 patients were randomized 1:1 to receive either 200 mg of intravenous pembrolizumab every 3 weeks for up to 35 treatment cycles plus oral axitinib at 5 mg twice daily (n = 432) or 50 mg of oral sunitinib once daily for the first 4 weeks of each 6-week cycle (n = 429).
In the ITT population, the combination had an OS rate of 90% versus 79% with sunitinib at 12 months and 74% versus 66%, respectively, at 24 months (HR, 0.68; 95% CI, 0.55-0.85; P < .001). The combination also led to a PFS rate of 60% at 12 months versus 48% with sunitinib and 38% versus 27%, respectively, at 24 months.

“Most patients will experience some stability or tumor shrinkage while on the [pembrolizumab/axitinib] regimen,” Rini noted. “In fact, most patients will have an objective response.” The confirmed objective response rate (ORR) was 60.2% in the pembrolizumab/axitinib arm and 39.9% in the sunitinib arm (P < .0001).

“Approximately 70% of patients who discontinued sunitinib received subsequent therapy and [roughly] 50% of those patients received subsequent immunotherapy therapy,” Rini added. “This really lends evidence that early immunotherapy and doublet [regimens] in kidney cancer are important.”

Another study that evaluated a novel immunotherapy combination in advanced RCC was the phase 2 HCRN GU16-260 trial (NCT03117309), which looked at nivolumab (Opdivo) and salvage nivolumab plus ipilimumab (Yervoy) in treatment-naïve patients. Although immunotherapy-based doublets such as nivolumab plus ipilimumab are commonly used to treat patients with RCC, monotherapies still remain largely unexplored in the space, according to Rini.

“Doublets have toxicities, especially when you [incorporate an agent] like ipilimumab,” Rini said. “Studies are now looking at treating patients with previously untreated kidney cancer with immune monotherapy, largely nivolumab. [Investigators] found that, if [nivolumab is given] alone and [patients] progress [on treatment] or have a lack of response, then they can add on ipilimumab.”

Patients who were given nivolumab monotherapy experienced an ORR of 31.7%, which Rini called “quite high” for this untested monotherapy.4

The first part of the trial involved nivolumab monotherapy, which would continue if patients responded. Patients who were stable or didn’t respond were then treated with nivolumab plus ipilimumab. Investigators found that hardly any patients could be salvaged through the doublet regimen. Ipilimumab/nivolumab led to an ORR of 13.3%, with no complete responses (CRs).

This is consistent with prior studies, which primarily saw ORR rates for nivolumab plus ipilimumab in the range of 4% to 20% (HCRN GU16-260, 13%; OMNIVORE, 4%; FRACION-RCC, 15%; TITAN RRC, 12%; salvage ipilimumab/nivolumab, 20%). CR rates were similar across the trials, with nearly every study producing a rate of 0%; TITAN RRC was the sole exception (3%).

“Patients generally need to receive combination therapy up front for maximal CR and benefit,” Rini said. “Unfortunately, pending biomarker work, we can’t get away with using monotherapy in most patients.”

**ANTIANDROGENS AND PSMA-BASED PET SCANS IN NONMETASTATIC PROSTATE CANCER**

In the prostate cancer space, the pivotal phase 3 ARAMIS trial (NCT02200614) evaluated darolutamide (Nubeqa) plus androgen deprivation therapy (ADT) versus placebo plus ADT in nonmetastatic castration-resistant prostate cancer (nmCRPC).

To be eligible for enrollment, patients needed a diagnosis of nmCRPC, along with a prostate-specific antigen (PSA) doubling time of 10 months or less. A total of 1509 patients were randomized 2:1 to receive either the darolutamide (Nubeqa) plus androgen deprivation therapy (ADT) versus placebo plus ADT.

The briefly mentioned SPARTAN study (NCT01946204) resembled the previously described studies in terms of patient eligibility and design. The trial compared the efficacy of apalutamide (Erleada) plus ADT with placebo/ADT and found that the agent significantly delayed the development of metastases. Not only that, but the trial validated MFS as a primary end point, according to Rini. The final data were also presented at the meeting and showed a significantly longer median OS of 73.9 months in the apalutamide arm versus 59.9 months in the placebo/ADT arm.5

Finally, in the CONDOR study (NCT03739684), investigators analyzed the impact of 18F-DCFPyL positron emission tomography (PET)/computed tomography (CT), or micro radiotracers, on the clinical management of patients with biochemically recurrent prostate cancer.6 PSMA-based imaging has shown great potential thus far within the space, according to Rini.

“If [a patient] has a rapidly rising PSA following prostatectomy, depending on the circumstance, standard imaging would be a CT of the abdomen and pelvis, and a bone scan,” Rini said. “In prostate cancer, we’ve always realized the clinical limitations of those scans. This disease has not been very easy to image with these conventional [modalities], hence these novel agents.”

Patients considered for the trial had a rising PSA following therapy (post radical prostatectomy, ≥ 0.2 ng/mL; post radiation therapy, ≥ 2 ng/mL). Patients who had negative
standard imaging were then able to receive the PSMA-based PET scan. After reviewing questionnaires that were filled out by the attending clinicians, investigators determined whether a change in intervention was reported.

Results showed that 65.9% of the patients enrolled on the trial who had previously received negative results from standard imaging had positive results following the PSMA-based PET scan. It was also found to have a correct localization rate of 85.6% from reader 1; 87.0%, reader 2; and 84.8%, reader 3. Based on these data, this type of imaging proved to be reliable among the 3 reviewers who tested it, Rini said. Following the results of these scans, 63.9% of evaluable patients had a change in intended care.

“A fair number of patients went from being relegated to noncurative systemic therapy [ie, hormone therapy] to salvage local therapy, which is potentially curative,” Rini said. “If the scan can provide us with the confidence to pursue potentially curative therapy, there is obviously great value in this [type of imaging].”

The modality has a long way to go, but according to Rini, PSMA is the best type of imaging within the space; however, integrating this modality into clinical practice remains a challenge.

In an interview with OncologyLive®, David P. Steensma, MD, the Edward P. Evans Chair in MDS Research, clinical director of the Center for Prevention of Progress at Dana-Farber Cancer Institute and an associate professor of medicine at Harvard Medical School both in Boston, Massachusetts, discussed the importance of evaluating eprenetapopt in the pivotal phase 3 study, the agent’s potential role in the MDS landscape, and some of the questions that remain in this setting.

**THE SMALL MOLECULE EPRENETAPOPT** (APR-246) is showing promising efficacy in patients with TP53-mutant myelodysplastic syndromes (MDS), a distinct molecular subgroup associated with poor outcomes, for which therapies have been unsuccessful in improving survival or delaying progression.1

TP53 gene mutations or chromosome 17 loss resulting in TP53 deletion present in up to 20% of MDS cases and impair function of the p53 tumor suppressor protein, which regulates DNA repair and cell division. Eprenetapopt, developed by Aprea Therapeutics, reactivates mutant p53 proteins by restoring wild-type p53 conformation and function to induce programmed cell death in patients with TP53-mutant disease.1

Results from a phase 1b/2 study (NCT03072043) of eprenetapopt in combination with azacitidine were encouraging. The doublet therapy elicited high response rates with an acceptable safety profile, providing the impetus for an ongoing, randomized, phase 3 trial (NCT03745716) of frontline eprenetapopt plus azacitidine versus azacitidine alone in 154 patients with TP53-mutant MDS (TABLE).2 The experimental agent, which holds FDA breakthrough therapy, fast track, and orphan drug designations in MDS, has also demonstrated preclinical efficacy in acute myeloid leukemia (AML) and ovarian cancer, among other malignancies.1

In an interview with OncologyLive®, David P. Steensma, MD, the Edward P. Evans Chair in

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**Investigator Looks to Novel Therapy to Advance TP53-Mutant MDS Landscape**

**by RACHEL NAROZNIAK, MA**

**Historically, how have TP53 mutations been targeted, and how effective have these therapeutic strategies been?**

TP53-mutant disease is one of the biggest unmet needs in MDS. When patients with TP53 mutations receive allogeneic hematopoietic cell transplantation, they tend to do more poorly than those without TP53 mutations, including frequent early relapses. We know that TP53 is enriched in therapy-related MDS, so people who have had treatment for some other type of nonmyeloid cancer many years later may develop MDS as a result of the treatment, and when that happens, it is often TP53-mutant disease.

TP53 mutations are associated with short survival, especially when both copies of TP53 are lost. Clinically, the TP53-mutant population is a very high risk group that is often treated with one of the DNA hypomethylating agents, either azacitidine or decitabine, and those lead to a high rate of response. But the response duration is often pretty short, with a median of 8 to 9 months, so the overall survival for these patients tends to be less than 1 year.

One thing that clinicians have been doing for TP53-mutant MDS is adding venetoclax [Venclexta]. The agent is approved for AML in combination with azacitidine, and the combination might help the response rate. We know that in the VIALE-A trial [NCT02993523], patients with AML who are treated with a hypomethylating agent plus venetoclax lived longer than those who just get the hypomethylating agent. But venetoclax isn’t approved for MDS, insurance doesn’t always pay for off-label use, and low blood counts are a real problem with venetoclax and can lead to complications. These are challenging problems and we really need new strategies for TP53-mutant disease.

**How do recent data support the use of this agent in the treatment of TP53-mutant MDS?**

One of the exciting things is that in the phase 1/2 trial, APR-246 was associated with quite a high overall and complete response rate, certainly higher than we would typically expect to see when looking at historical controls of azacitidine monotherapy. Anytime patients are enrolled in uncontrolled clinical trials, though, we wonder, “Are they just
healthier than the general population? Were they destined to do well otherwise?” So the uncontrolled data are difficult to interpret but are encouraging. Still, in MDS, we’ve been burned many times by phase 2 trials in which interventions looked like they had a high response rate, were then taken into phase 3, and showed no improvement.

Some examples are the combination of azacitidine with histone deacetylase inhibitors, such as vorinostat [Zolinza] or entinostat. More than 4 randomized trials of azacitidine with deacetylase inhibitors showed no benefit compared to azacitidine monotherapy, just more adverse events with the combination. Azacitidine plus lenalidomide [Revlimid] also looked pretty good in a phase 2 study but didn’t pan out in the phase 3 investigation [NCT01522976]. The phase 3 trial that is testing APR-246 plus azacitidine versus azacitidine alone [NCT03745716] has now completed accrual and hopefully will report out by the end of the year. It is a really important study for trying to understand if this is a viable strategy.

**Q** Please explain the rationale for combining these 2 agents.

Both azacitidine and decitabine are important standards of care for patients with MDS. Those are the backbones of therapy, and azacitidine is the only agent that’s been shown to improve overall survival for higher-risk patients in a randomized trial—so patients deserve to have exposure to this drug.

The reason for combining azacitidine with APR-246 is that reactivating TP53 alone only may partially sensitize the cell to dying if it is an abnormal cell. Normally if there’s DNA injury detected in a cell, that cell would be programmed to die, and that program would be mediated by p53. If you restore a p53 function in an abnormal cell but there’s not enough DNA damage to the cell, then the cell may still survive. If you combine APR-246 with an agent that causes DNA damage or cellular stress like azacitidine, then that intact p53 may finally be able to sound the alarm and kill the cell, so to speak.

In MDS, we’ve seen a number of trials where there was no logic behind combining agents with azacitidine. Previously, it’s been, “Oh, our drug has a little bit of effectiveness, or even no effectiveness, but maybe it will be better if we combine it with azacitidine,” and that’s kind of a desperate move. Here, as with venetoclax—which also sensitizes cells to death but doesn’t have a lot of independent activity on its own in myeloid disorders—there’s a real rationale for combination.

**Q** What do we know about the safety profile of eprenetapopt?

From what we’ve seen so far, APR-246 has a favorable safety profile. The recurrent toxicity that we’ve seen is a peculiar form of neuropathy where patients may feel altered sensation, such as their skin feeling especially sensitive. They may feel like ants are crawling on their skin or other peculiar sensations, and this usually gets better with prochlorperazine, which is a widely used anti-nausea medicine. So, for the most part, that adverse event has been manageable.

I was impressed in the phase 1/2 experience by just how well patients did with the drug. Overall, APR-246 didn’t seem to cause a lot of trouble, other than the neuropathy. We will see in the randomized comparison how the toxicity patterns compare to azacitidine alone, and that will provide more information. My suspicion is that we’ll see more neuropathy with the combination group, but probably not a lot of other differences in terms of adverse events.

**Q** What challenges remain in other subtypes of MDS?

There are a number of unmet needs for patients with MDS outside of TP53-mutant disease. In the higher-risk population, for the majority of patients, hypomethylating agents will either stop working within 1 to 2 years or they weren’t working in the first place. We don’t have a second-line therapy that’s useful and has been shown to improve survival or delay disease progression, so that’s a big unmet need. In fact, the long-awaited, randomized trial [INSPIRE; NCT02562443] of rigosertib just reported out in that post hypomethylating agent setting, and data showed that rigosertib failed to improve survival compared with physician’s choice of alternate therapy.

The second big unmet need is for the lower-risk patients, whose main problem is low blood counts that could cause them to be transfusion dependent on a regular basis, which is quite inconvenient for them. We had luspatercept [Reblozyl] approved for MDS with ring sideroblasts and SF3BI mutations in April, which was the first new drug approved for an MDS indication in 14 years. However, luspatercept only helps a subset of patients, and the approval was only for those with ring sideroblasts, which is 15% to 20% of patients at most. There are a lot of other patients with low blood counts that either aren’t good candidates for luspatercept or have been failed by luspatercept, and the question becomes, “How can we improve counts for them?”

These are probably the 2 biggest needs, but there are others. For the transplant population, how to prevent relapse after transplant is also a key question.

**REFERENCES**


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**TABLE.** Phase 1/2 Findings: Efficacy of Eprenetapopt Plus Azacitidine

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>APR-246 + azacitidine (n = 45)&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>85%</td>
</tr>
<tr>
<td>For MDS/AML (n = 41)</td>
<td>88%</td>
</tr>
<tr>
<td>For MDS/MPN (n = 4)</td>
<td>75%</td>
</tr>
<tr>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>53%</td>
</tr>
<tr>
<td>Marrow CR + hematologic improvement</td>
<td>18%</td>
</tr>
<tr>
<td>Hematologic improvement alone</td>
<td>7%</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>9%</td>
</tr>
<tr>
<td>Median time to response, months (range)</td>
<td>2.1 (0.1-5.4)</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>6.5</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; CR, complete response; DOR, duration of response; IWG, International Working Group; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms.

<sup>4</sup>Forty-five of the 55 patients enrolled were evaluable for response at a median follow-up of 10.5 months.
INDICATION
NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

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

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

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

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

Drug Interactions
Effect of Other Drugs on NUBEQA – Concomitant use of NUBEQA...
NUBEQA®—Focus on both MFS and tolerability

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone

More than double the median MFS with NUBEQA + ADT* vs 18 months with ADT alone†

( HR: 0.41; 95% CI: 0.34-0.50; P=0.0001) *95% CI: 34.3-NR. †95% CI: 15.5-22.3.

PROVEN TOLERABILITY

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

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

NUBEQA®—proven to extend MFS, now with statistically significant OS

Metastasis-free survival (MFS) was the primary endpoint. Overall survival (OS) was a key secondary endpoint. OS data were not mature at time of first analysis (57% of the required number of events).

At final analysis, OS was statistically significant but median not reached: HR: 0.69 (95% CI: 0.53-0.88); P=0.003.

SAME RATE OF PERMANENT DISCONTINUATION

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, 18F-fluorodeoxyglucose positron emission tomography, or death.

Effects of Other Drugs on NUBEQA

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer increases darolutamide exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

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

Visit NUBEQAhcp.com

Start new patients with up to 2 months free.*

with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor decreases darolutamide exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

Effects of NUBEQA on Other Drugs – NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of
1 INDICATIONS AND USAGE
NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS
None.

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

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1, 8.3)].

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

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1% of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA. Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a ≥ 2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

### Table 1: Adverse Reactions in ARAMIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥ 3 (%)</th>
<th>All Grades (%)</th>
<th>Grades ≥ 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUBEQA (n=954)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>0.6</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0.1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (n=554)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

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

Combination use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs
Breast Cancer Resistance Protein (BCRP) Substrates
NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

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

Animal embryo-fetal developmental toxicity studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

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

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

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

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

8.5 Geriatric Use
Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment
Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m²). The effect of end-stage renal disease (eGFR ≤15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment
Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE
There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
**NONCLINICAL TOXICOLOGY**

13 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hyposperma, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

**17 PATIENT COUNSELING INFORMATION**

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

Infertility

Advise male patients that NUBEQA may impair fertility [see Use in Specific Populations (8.3)].

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Community Practice Provides Model for Finding New Revenue in COVID-19 Era
by BARRY FORTNER, PhD

INDEPENDENT COMMUNITY oncology practices are critical to the fabric of cancer care in the United States. They allow patients nationwide to receive high-quality, affordable, and accessible care in the communities where they live and work.1 While the coronavirus disease 2019 (COVID-19) pandemic is highlighting how a community practice is the best source for patients to receive care close to home, it is also presenting several challenges for practices and their patients.

Patients—either nervous to access care or facing increased barriers—canceled appointments and delayed screening visits.2 On average, oncologists saw a 40% drop in weekly visits from new patients, and cancellations doubled during the first few months of the pandemic’s stay-at-home orders.3 Lower patient volumes not only prevented oncologists and other specialists throughout the country from being able to fully support their communities but also created new financial constraints for these providers. According to 1 survey, 50% of private practices had to furlough office staff, and almost 25% were forced to make permanent layoffs.3 As a result, practices needed to find new ways to provide the care their community needed and to maintain revenues, allowing them to remain viable.

Some practices already had a business strategy in place that positioned them for success. For example, Gabrail Cancer Center in Canton, Ohio, is thriving amid the pandemic because of the trust and partnerships it has built over the years to meet the needs of a rural town that is home to several food processing plants and an Amish community. Gabrail’s ability to look broadly at regional needs of local patients, businesses, and the community at large provides a model from which many practices can learn.

THE HISTORY: EMBEDDING A PRACTICE INTO THE COMMUNITY
When Nashat Gabrail, MD, founded Gabrail Cancer Center in 1990, he immediately recognized the importance of building connections with other local businesses and meeting potential patients where they already were. Knowing his Canton, Ohio, community is primarily an industrial and agricultural area with many food processing plants and home to a large Amish community, he saw an opportunity to help meet the health care needs of residents and to create a thriving oncology practice with multiple revenue streams.

He approached the large local food manufacturers and, over time, worked with them to establish on-site clinics at their facilities that provided both preventive and acute care, and also offered oncology screenings and consultations. The practice has maintained some of these clinics for close to a decade, and as COVID-19 began to spread—impacting manufacturing plants (which are densely populated) at greater rates than other businesses—Gabrail was well positioned to provide support.

Early on in the practice’s history, Gabrail’s team built relationships within the local Amish community and worked to gain their trust by offering many of them a nearby, affordable option for cancer care.

In addition, Gabrail Cancer Center implemented a clinical trials program to give local patients convenient access to the most innovative therapies without having to venture hours away to cancer research sites or large hospitals.

THE OPPORTUNITY: FALLING CANCER SCREENINGS BUT GROWING HEALTH CARE NEEDS
Many oncology practices across the country saw new patient referrals fall at the start of the pandemic as screening appointments dropped weekly, according to 1 survey.4 Clinical trial programs were also shutting down. According to a recent American Cancer Society survey, more than 50% of cancer researchers reported that their work was temporarily put on hold due to the pandemic.5 At the same time, food manufacturing facilities across the country were finding themselves at particular risk for COVID-19 outbreaks due to the density of their workforce. Counties with food processing plants were experiencing infection rates higher than 75% of other US counties.6 These outbreaks were threatening the health of the workers and their families, and they were causing facilities to shut down, leading to food shortages throughout the United States.

To compound these issues, Amish populations across Ohio experienced spikes in...
COVID-19 cases. These outbreaks affected the Amish community in Stark County, Ohio, and in surrounding counties with limited access to local care.

Gabrail saw an opportunity to help address these issues and to protect the long-term viability of his practice: He needed to evolve, invest, and expand.

**THE APPROACH:**
**TAILORING SERVICES BASED ON NEED; ENSURING SUCCESS**

Gabrail leveraged his practice’s existing local partnerships to expand his services, based on the specific needs of managing the spread of COVID-19 as well as its indirect consequences. Gabrail began working with local manufacturers to screen employees according to the Centers for Disease Control and Prevention COVID-19 guidelines.

Gabrail and his team offered temperature checks to employees before they entered the food plant, at their lunchtime, and again when their shift was complete. Should an employee show any symptoms of illness, they were moved to an off-site, outdoor clinic for flu and coronavirus testing.

Gabrail even created a hotline for the food plant employees that they could call to be assessed before reporting to work. And nurses helped patients complete online questionnaires to determine illness or mental health issues that could be exacerbated by the pandemic. These added measures helped ensure the staff was at low risk for infection yet still maintained their essential duties—avoiding supply-chain disruption.

Ultimately, Gabrail avoided practice constriction and, instead, expanded his staff to provide health assessments for more than 2200 employees in the Canton area—which often included 3 assessments per employee, per shift. Recently, Gabrail Cancer Center also expanded its offerings to other states to do mass testing and provide services for more food plants.

Gabrail also had the opportunity to strengthen his relationships with the local Amish community when it experienced a COVID-19 outbreak. When local Amish learned that Gabrail has established clinics at local companies, they, too, turned to his practice. Gabrail Cancer Center would assess their symptoms remotely and if required, would send staff to do viral testing and treat them.

Gabrail also expanded existing services to help members of the Amish community continue to get access to necessary cancer care without fear of contraction. For instance, his cancer center delivered prescription drugs to Amish homes for convenience and to minimize COVID-19 exposure. For current patients, Gabrail purchased a 16-seat van to transport Amish patients receiving chemotherapy and other infusions to ensure they could safely continue treatment.

Also important to both the Amish and larger community was Gabrail Cancer Center’s commitment to maintaining its access to clinical trials. The center kept its program open and added new clinical trials to make up for the research sites that had to close amid the pandemic. As a result, it became the alternative referral site for practice and academic centers.

**THE OUTCOME:**
**INCREASING PATIENT VOLUME; PROTECTING A VIABLE BUSINESS**

By July 2020, Gabrail Cancer Center was supporting 8 food processing plants on a 24/7 basis. Since partnering with Gabrail, all the plants that implemented his screening and health care support have avoided shutdowns and stayed open.

While many US practices were suffering from decreased patient volume, Gabrail Cancer Center reported an uptick in new patients seeking clinical trials. And with this ongoing demand for care and services from local communities and businesses, Gabrail hired more than 43 highly qualified providers who had been furloughed or laid off from other local hospitals.

Gabrail also leveraged the surge in need and temporary revenue to help ensure his practice will remain viable. He was even able to complete the construction of a new building with a drive-through for his retail pharmacy in July. Previously, the pharmacy had been located in a small space inside the cancer center.

And, potentially most important for the future, Gabrail further positioned himself within the community as a connected, embedded provider who understands the unique needs of the region.

**THE TAKEAWAY:**
**LEARNING FROM THE MODEL AND LOOKING AHEAD**

Not every practice will be able to do what Gabrail Cancer Center did, but the broader implications of its approach offer learnings for all community oncologists. Gabrail’s ability to understand and assess the region’s most critical needs and think creatively about how its services could fill those gaps—even temporarily—is an important lesson. All community-based care providers have the opportunity to use their position and local knowledge to adapt to whatever threatens their community’s health.

“Community providers should always be considering other revenue streams for their practice,” Gabrail said. “This pandemic represented an unexpected challenge for us, and we are providing a service to our community and the businesses, helping to keep our own community healthier.”

As practices have begun to return to more “normal” day-to-day operations in the face of growing numbers of COVID-19 infections, patients may continue resisting care. They may think they are protecting their health by staying home and avoiding centralized points of care, like community practices. But thousands of excess cancer deaths are expected to occur over the next decade as a result of missed screenings, delays in diagnosis, and reductions in oncology care caused by the COVID-19 pandemic.

It’s imperative that oncology practices proactively engage their patients and address their fears. Through social channels and their marketing efforts, oncology practices can reinforce that now is the time for patients to prioritize their health. Oncology practices can also connect with and demonstrate a commitment to their patients through surveys and follow-up phone calls.

Community-based care providers also need to share all new protocols and procedures they are implementing to ensure patients can be safely seen and treated.

Barry Fortner, PhD, is senior vice president and president of Specialty Physician Services at AmerisourceBergen.

For a full list of references, see the article at Onclive.com.
Americans’ insurance coverage was precarious even before the beginning of the coronavirus disease 2019 (COVID-19) pandemic and the economic crisis that kicked off, according to a recent survey.

In the first half of 2020, 43.4% of adults aged 19 to 64 were inadequately insured, according to the survey conducted by The Commonwealth Fund. This was not a statistical change from a previous survey in 2018. Data collection started January 14, 2020, before the pandemic broke out, and continued through June 5, 2020.1

The Commonwealth Fund survey considered people to be underinsured if out-of-pocket expenses (not including premiums) were equal to 10% or more of household income or 5% of household income for those living under 200% of the federal poverty level, which is currently $25,520 for an individual or $52,400 for a family of 4.

The survey found that people who were enrolled in plans through the Affordable Care Act marketplaces were underinsured at the highest rates. But about one-fourth of adults in employer plans also were underinsured.

The uninsured rate for adults was 12.5%, while 9.5% of adults were insured but had a gap in this coverage over the past year, and 21.3% were underinsured. This also was statistically unchanged from the 2018 survey.

People of color, small business workers, people with low incomes, and younger adults have the highest uninsured rates. The survey found that about one-third of Latino adults, small business workers, and low-income adults were either uninsured or had spent time uninsured in the past year.

“The survey shows a persistent vulnerability among US working-age adults in their ability to afford coverage and health care,” Sara Collins, lead author of the study and The Commonwealth Fund vice president for health care coverage and access, said in a news release. “That vulnerability could worsen if the COVID-19 pandemic and related economic downturn continue. Coverage inadequacy is compromising people’s ability to get the care they need and leaving many with medical debt at a moment of widespread health and financial insecurity, and an uncertain future.”

The survey found underinsured and uninsured people often delay getting needed treatment and medications because of cost. In fact, 56% of those who were uninsured and 43% of those who were underinsured either did not fill a prescription, skipped a test or treatment, or did not visit a doctor or get specialist care because of cost (FIGURE).

The survey also found that many adults are struggling to pay their medical bills, and those with inadequate coverage have a harder time doing so. One-fourth of respondents with adequate coverage for the full year prior to the survey had medical bill problems or debt in the past year. In the survey, 37% of respondents say they have depleted their savings to pay their bills, while 26% reported they were unable to pay for basic necessities such as food, heat, or rent.

REFERENCE

FIGURE. Uninsured or Underinsured Adults Often Avoid or Delay Getting Needed Health Care and Medications1
Percent of adults ages 19-64 who had any of 4 access problems in the past year because of cost

<table>
<thead>
<tr>
<th>Problem</th>
<th>Total</th>
<th>Insured all year, not underinsured</th>
<th>Insured all year, underinsured</th>
<th>Uninsured any time in the past year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not fill prescription</td>
<td>21%</td>
<td>14%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Skipped recommended test, treatment, or follow-up</td>
<td>19%</td>
<td>10%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Had a medical problem; did not visit doctor or clinic</td>
<td>21%</td>
<td>12%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Did not get needed specialist care</td>
<td>15%</td>
<td>9%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Had at least 1 of these access problems because of cost</td>
<td>35%</td>
<td>23%</td>
<td>43%</td>
<td>56%</td>
</tr>
</tbody>
</table>

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The state of cancer treatment today, with insights for tomorrow.

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  Washington, DC

- **William K. Oh, MD**
  Tisch Cancer Institute
  New York, NY

- **Tiffany A. Traina, MD**
  Weill Cornell Medicine
  New York, NY

** REGISTRATION FEES **

<table>
<thead>
<tr>
<th></th>
<th>3-DAY</th>
<th>1-DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians</td>
<td>$399</td>
<td>$135.66</td>
</tr>
<tr>
<td>Fellows</td>
<td>$179</td>
<td>$60.86</td>
</tr>
<tr>
<td>Nurses, PAs, other HCPs</td>
<td>$179</td>
<td>$60.86</td>
</tr>
<tr>
<td>Industry</td>
<td>$675</td>
<td>$60.86</td>
</tr>
</tbody>
</table>

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Palliative Care for Young Adults Is a Growing Reality in CRC

by RAJIV AGARWAL, MD; AND CATHY ENG, MD

YOUNG ADULTS REPRESENT AN expanding and vulnerable subset of patients with colorectal cancer (CRC). It is estimated that in 2020, those less than 50 years old will make up 12% of newly diagnosed cases and 7% of CRC-related deaths in the United States.1 Although most younger patients received diagnoses of cancer of the rectum or distal colon, incidence rates are increasing across all CRC anatomic subsites. In addition, over a 10-year period (2007-2016), the number of advanced-staged diagnoses in young adults in the United States grew 2.7% annually for regional disease and 2.5% for distant disease.1,2 Compared with those aged 50 to 64 years and 65 years or older, patients in the young adult age group have a greater percentage of de novo metastatic disease. This rising incidence of early-onset advanced CRC is unfortunately, yet expectedly, mirrored by an upward trend in the young adult CRC mortality rate.1 These findings are not unique to the United States; the incidence of CRC among young adults has concurrently increased in several other high-income countries,3 suggesting a global epidemiological shift.

As a younger population of patients with CRC becomes a growing reality, it is essential to study and identify potential differences in underlying tumor biology, molecular profiling, disease characteristics, clinical presentation, and treatment response.4-6 It is equally critical to address the unmet psychosocial, developmental, informational, and palliative care needs of these patients.7,8 Caring for younger patients with advanced CRC is challenging for oncologists, palliative care specialists, nursing professionals, pharmacists, social workers, and family caregivers partly because CRC, which historically affected an older population, can manifest earlier than expected and at advanced stages, even without hereditary warning. After decades of steadily growing incidence among young adults, a disease that was once unexpected has become more probable, and what was once rare is now more common.

FULFILLING A NEED FOR YOUNG ADULT PATIENTS

Palliative and supportive care in oncology can help people of all ages live and cope with cancer and ensure that health care–related decisions align with personal values and goals. Specifically, palliative care can mitigate symptom burden, improve quality of life, and even extend survival; however, these benefits were originally demonstrated in older patients.9-11 Prior palliative care research in the adolescent and young adult (AYA) cancer population (aged 15-39 years) has shown that younger patients not only face the gravity of their illness and disease-related implications but also must contend with their own psychosocial development and existential maturity relative to their healthy peers.12-15

Young adults vary in their independence and autonomy, relationships with others and society, and concept of identity and formulation of values, all of which are dependent on precancer life experiences and may drastically change upon receiving a cancer diagnosis. In addition, younger patients may fear and worry about an un-lived future or uncompleted life and the effect of their death on loved ones. As a result, these patients require proactive attention and resources for psychosocial distress, spirituality and existential concerns, physical and mental wellness, fertility and sexuality, genetic counseling, financial guidance, and support for academic and/or professional ambitions. Cancer treatment planning for young adults should therefore promote the achievement of personal, developmental, and major life milestones whenever possible.12-17

Recent studies have focused on characterizing the priorities and experiences of young adults with advanced-stage cancer, including assessment of prognostic and end-of-life communication needs. Themes from a qualitative analysis of AYA patients with metastatic cancer show that young adults may seek aggressive cancer treatment, but also endorse a lack of prognostic clarity and want more support to accept their mortality.18 Prognostic communication can be difficult for any patient facing a serious illness, but perhaps more so when disease presents earlier than expected, such as in the case of young adult CRC. Ongoing conceptual and practical models are being developed to enhance serious illness communication for young adults. Conversations about prognosis should start at the time of diagnosis and be conducted in iterative fashion, personalized for each individual’s cancer type, information preferences, and developmental context.19-20

Despite recognition of the importance of prognostic discussions for AYAs, palliative care consultations and hospice care referrals occur late, if at all.21-23 Such utilization patterns may be partly explained by health care providers in oncology, who report that introducing and providing palliative care for younger adults...
is more challenging than doing so for older adults. Oncology providers may feel more tragedy, emotional closeness and empathy, and uncertainty in how to engage with a young patient’s family.24 Even when oncologists and palliative care specialists know from experience what to say or how to approach prognostic discussions for cancers that typically affect specific age groups, when disease shifts earlier, it creates a unique set of communication issues that cannot be overlooked.

Data for CRC-specific patient-reported outcomes in the young adult population are limited. Larger studies that have measured quality of life in AYAs have minimal to no representation of young-onset CRC.25,26 Two analyses have examined treatment-decision making patterns, related worries, and information-seeking behavior in young adult patients with CRC (FIGURE).27,28 In 148 patients aged 21 to 40 years in which 80% had CRC, decision-making preferences were similar to those of middle-aged patients (age 41-60 years), but younger adults had significantly more concern for spending time away from family.27 In a large international survey comparing 455 patients with young-onset CRC to 670 with average-onset CRC, both groups sought health information with similar frequency; however, younger patients significantly differed by using the internet as a first source and downloading smartphone cancer and wellness apps for personal support.28 Unlike other AYA cancers such as hematologic malignancies, sarcomas, germ-cell tumors, and breast cancer, young adult CRC is still a relatively novel and growing disease entity, presenting unique psychosocial, communication, and practical challenges for oncologists and patients.

Patients with young-onset CRC deserve our attention to optimize their health and wellbeing in the context of their lives and personal development. Age-appropriate and tailored palliative care interventions are needed to support this emerging patient demographic. 

---

**FIGURE. Decision-Making Influences Regarding Cancer Treatment**27

Which statement best describes the role that your family played when decisions about treatment for your cancer were made?

<table>
<thead>
<tr>
<th>Patients’ age</th>
<th>Mating-Decisions</th>
<th>N = 148</th>
<th>N = 444</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 to 40 yrs</td>
<td>You made the decisions with little or no input from your family.</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>41 to 60 yrs</td>
<td>Your family made the decisions after considering your opinion or with little or no input from you.</td>
<td>30%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Worried about...

- Adverse events from treatment
- Cost of treatment
- Taking time away from family
- Taking time away from work
- Transportation to treatment

Patients aged 21 to 40 years

<table>
<thead>
<tr>
<th>Mating-Decisions</th>
<th>N = 148</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events from treatment P = .20</td>
<td>25%</td>
</tr>
<tr>
<td>Cost of treatment P = .96</td>
<td>40%</td>
</tr>
<tr>
<td>Taking time away from family P = .002</td>
<td>37%</td>
</tr>
<tr>
<td>Taking time away from work P = .31</td>
<td>46%</td>
</tr>
<tr>
<td>Transportation to treatment P = .71</td>
<td>20%</td>
</tr>
</tbody>
</table>

Patients aged 41 to 60 years

<table>
<thead>
<tr>
<th>Mating-Decisions</th>
<th>N = 444</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events from treatment P = .20</td>
<td>30%</td>
</tr>
<tr>
<td>Cost of treatment P = .96</td>
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<td>52%</td>
</tr>
<tr>
<td>Taking time away from work P = .31</td>
<td>51%</td>
</tr>
<tr>
<td>Transportation to treatment P = .71</td>
<td>19%</td>
</tr>
</tbody>
</table>
NOW APPROVED

MONJUVI®
tafasitamab-cxix | 200mg
for injection, for intravenous use

FDA-approved monoclonal antibody in combination with lenalidomide for adult patients with R/R DLBCL who have received at least one prior therapy

INICATIONS & USAGE
MONJUVI (tafasitamab-cxix), in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

IMPORTANT SAFETY INFORMATION
Contraindications
None.

Warnings and Precautions
Infusion-Related Reactions
MONJUVI can cause infusion-related reactions (IRR). In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypertension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication. Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

Myelosuppression
MONJUVI can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In L-MIND, Grade 3 neutropenia occurred in 25% of patients, thrombocytopenia in 12% and anemia in 7%. Grade 4 neutropenia occurred in 25% and thrombocytopenia in 6%. Neutropenia led to treatment discontinuation in 3.7% of patients.

Monitor complete blood counts (CBC) prior to administration of each treatment cycle and throughout treatment. Monitor patients with neutropenia for signs of infection. Consider granulocyte colony stimulating factor (G-CSF) administration. Withhold MONJUVI based on the severity of the adverse reaction. Refer to the lenalidomide prescribing information for dosage modifications.

Infections
Fatal and serious infections, including opportunistic infections, occurred in patients during treatment with MONJUVI and following the last dose.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (16%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

Embryo-Fetal Toxicity
Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women, because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Adverse Reactions
The most common adverse reactions (≥20%) were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to MORPHOSYS US INC. at (844) 667-1992.

Please see the Brief Summary of Prescribing Information on the following pages.
**BEST OVERALL RESPONSE RATE IN PATIENTS WITH R/R DLBCL (N=71)**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>37% CR</th>
<th>55% ORR</th>
</tr>
</thead>
</table>

**L-MIND STUDY DESIGN**
- L-MIND was an open-label, multicenter, single-arm study that evaluated efficacy and safety of MONJUVI in combination with lenalidomide followed by MONJUVI monotherapy in adult patients with R/R DLBCL after 1 to 3 prior systemic DLBCL therapies, including a CD20-containing therapy. The median number of prior therapies was 2
- Enrolled patients at the time of the trial were not eligible for or refused ASCT
- Efficacy was established in 71 patients with DLBCL (confirmed by central laboratory) based on best ORR (defined as the proportion of complete and partial responders) and DoR

**DURATION OF RESPONSE IN PATIENTS WITH R/R DLBCL (N=71)**

> Median DoR: 21.7 months (range: 0, 24)

*Assessed by an Independent Review Committee.

**SAFETY PROFILE**
- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in other clinical trials of another drug and may not reflect the rates observed in practice
- Serious adverse reactions occurred in 52% of patients who received MONJUVI
  - Serious adverse reactions in ≥6% of patients included infections (26%) including pneumonia (7%), and febrile neutropenia (6%)
  - Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebrovascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%), and sudden death (1.2%)
- Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%
  - The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections (5%), nervous system disorders (2.5%), respiratory, thoracic, and mediastinal disorders (2.5%)
- Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%
  - The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%)

For more details on Adverse Reactions, refer to the full Prescribing Information.

**REFERENCE:** 1. MONJUVI Prescribing Information. Boston, MA: MorphoSys.

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MONJUVI® (tafasitamab-cxix)

Initial U.S. Approval: 2020

INDICATIONS AND USAGE
MONJUVI, in combination with lenalidomide, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

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

CONTRAINdications
None.

WARNINGS AND PRECAUTIONS

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MONJUVI can cause infusion-related reactions. In L-MIND, infusion-related reactions occurred in 6% of the 81 patients. Eighty percent of infusion-related reactions occurred during cycle 1 or 2. Signs and symptoms included chills, flushing, dyspnea, and hypotension. These reactions were managed with temporary interruption of the infusion and/or with supportive medication.

Premedicate patients prior to starting MONJUVI infusion. Monitor patients frequently during infusion. Based on the severity of the infusion-related reaction, interrupt or discontinue MONJUVI. Institute appropriate medical management.

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Fatal and/or serious infections including opportunistic infections have occurred in patients during treatment with MONJUVI and following the last dose.

In L-MIND, 73% of the 81 patients developed an infection. The most frequent infections were respiratory tract infection (24%), urinary tract infection (17%), bronchitis (9%), nasopharyngitis (10%) and pneumonia (10%). Grade 3 or higher infection occurred in 30% of the 81 patients. The most frequent grade 3 or higher infection was pneumonia (7%). Infection-related deaths were reported in 2.5% of the 81 patients.

Monitor patients for signs and symptoms of infection and manage infections as appropriate.

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Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose.

MONJUVI is initially administered in combination with lenalidomide. The combination of MONJUVI with lenalidomide is contraindicated in pregnant women, because lenalidomide can cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

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

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
The safety of MONJUVI was evaluated in L-MIND. Patients (n=81) received MONJUVI 12 mg/kg intravenously in combination with lenalidomide for maximum of 12 cycles, followed by MONJUVI as monotherapy until disease progression or unacceptable toxicity as follows:

- Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle;
- Cycle 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle;
- Cycles 4 and beyond: Days 1 and 15 of each 28-day cycle.

Among patients who received MONJUVI, 57% were exposed for 6 months or longer, 42% were exposed for greater than one year, and 24% were exposed for greater than two years.

Serious adverse reactions occurred in 52% of patients who received MONJUVI. Serious adverse reactions in ≥6% of patients included infections (26%) including pneumonia (7%), and febrile neutropenia (6%). Fatal adverse reactions occurred in 5% of patients who received MONJUVI, including cerebral vascular accident (1.2%), respiratory failure (1.2%), progressive multifocal leukoencephalopathy (1.2%) and sudden death (1.2%).

Permanent discontinuation of MONJUVI or lenalidomide due to an adverse reaction occurred in 25% of patients and permanent discontinuation of MONJUVI due to an adverse reaction occurred in 15%. The most frequent adverse reactions which resulted in permanent discontinuation of MONJUVI were infections and infestations (5%), nervous system disorders (2.5%), respiratory, thoracic and mediastinal disorders (2.5%).

Dosage interruptions of MONJUVI or lenalidomide due to an adverse reaction occurred in 69% of patients and dosage interruption of MONJUVI due to an adverse reaction occurred in 65%. The most frequent adverse reactions which required a dosage interruption of MONJUVI were blood and lymphatic system disorders (41%), and infections (27%).

The most common adverse reactions ≥ 20% were neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.

| Table 3: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND |
|-------------------------------------------------|-----------------|------------------|
| **Adverse Reaction**                           | **All Grades (%)** | **Grade 3 or 4 (%)** |
| Blood and lymphatic system disorders          |                  |                  |
| Neutropenia                                    | 51               | 49               |
| Anemia                                         | 36               | 7                |
| Thrombocytopenia                               | 31               | 17               |
| Febrile neutropenia                            | 12               | 12               |
| General disorders and administration site conditions |            |                  |
| Fatigue*                                       | 38               | 3.7              |
| Pyrexia                                        | 24               | 1.2              |
| Peripheral edema                               | 24               | 0                |
| Gastrointestinal disorders                     |                  |                  |
| Diarrhea                                       | 36               | 1.2              |
| Constipation                                   | 17               | 0                |
| Nausea                                         | 15               | 0                |
| Vomiting                                       | 15               | 0                |
| Respiratory, thoracic and mediastinal disorders |                  |                  |
| Cough                                          | 26               | 1.2              |
| Dyspnea                                        | 12               | 1.2              |
| Infections                                     |                  |                  |
| Respiratory tract infection*                   | 24               | 4.9              |
| Urinary tract infection*                       | 17               | 4.9              |
| Bronchitis                                     | 16               | 1.2              |
| Metabolism and nutrition disorders             |                  |                  |
| Decreased appetite                             | 22               | 0                |
| Hypokalemia                                    | 19               | 6                |
| Musculoskeletal and connective tissue disorders|                  |                  |
| Back pain                                      | 19               | 2.5              |
| Muscle spasms                                  | 15               | 0                |

* Fatigue includes asthenia and fatigue
+ Respiratory tract infection includes: lower respiratory tract infection, upper respiratory tract infection, respiratory tract infection
* Urinary tract infection includes: urinary tract infection, Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal

Table 3 summarizes the adverse reactions in L-MIND. Clinically relevant adverse reactions in <10% of patients who received MONJUVI were:

- **Blood and lymphatic system disorders**: lymphopenia (6%)
- **General disorders and administration site conditions**: infusion-related reaction (6%)
- **Infections**: sepsis (4.9%)
- **Investigations**: weight decreased (4.9%)
- **Musculoskeletal and connective tissue disorders**: arthralgia (9%), pain in extremity (9%), musculoskeletal pain (2.5%)
- **Neoplasms benign, malignant and unspecified**: basal cell carcinoma (1.2%)
- **Nervous system disorders**: headache (9%), paresthesia (7%), pyrexia (6%)
- **Respiratory, thoracic and mediastinal disorders**: nasal congestion (4.9%), exacerbation of chronic obstructive pulmonary disease (1.2%)
- **Skin and subcutaneous tissue disorders**: erythema (4.9%), alopecia (2.5%), hyperhidrosis (2.5%)
Table 4 summarizes the laboratory abnormalities in L-MIND.

**Table 4: Select Laboratory Abnormalities (>20%) Worsening from Baseline in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma Who Received MONJUVI in L-MIND**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase increased</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Aspartate Aminotransferase increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated Partial Thromboplastin Time</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

The denominator used to calculate the rate was 74 based on the number of patients with a baseline value and at least one post-treatment value.

**Immunogenicity**

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

Overall, no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety profile of tafasitamab-cxix were observed in 2.5% of 81 patients with relapsed or refractory DLBCL with pre-existing anti-tafasitamab antibodies in L-MIND.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, MONJUVI may cause fetal B-cell depletion when administered to a pregnant woman. There are no available data on MONJUVI use in pregnant women to evaluate for a drug-associated risk. Animal reproductive toxicity studies have not been conducted with tafasitamab-cxix.

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

MONJUVI is administered in combination with lenalidomide for up to 12 cycles. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide prescribing information for additional information. Lenalidomide is only available through a REMS program.

**Clinical Considerations**

**Fetal/Neonatal Adverse Reactions**

Immunoglobulin G (IgG) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, MONJUVI may cause depletion of fetal CD19 positive immune cells. Defer administering live vaccines to neonates and infants exposed to tafasitamab-cxix in utero until a hematology evaluation is completed.

**Data**

**Animal Data**

Animal reproductive studies have not been conducted with tafasitamab-cxix. Tafasitamab-cxix is an IgG antibody and thus has the potential to cross the placental barrier permitting direct fetal exposure and depleting fetal B lymphocytes.

**Lactation**

**Risk Summary**

There are no data on the presence of tafasitamab-cxix in human milk or the effects on the breastfed child or milk production. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to MONJUVI are unknown. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with MONJUVI and for at least 3 months after the last dose. Refer to lenalidomide prescribing information for additional information.

**Females and Males of Reproductive Potential**

MONJUVI can cause fetal B-cell depletion when administered to a pregnant woman.

**Pregnancy Testing**

Refer to the prescribing information for lenalidomide for pregnancy testing requirements prior to initiating the combination of MONJUVI with lenalidomide.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment with MONJUVI and for at least 3 months after the last dose. Additionally, refer to the lenalidomide prescribing information for additional recommendations for contraception.

**Males**

Refer to the lenalidomide prescribing information for recommendations.

**Pediatric Use**

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

**Geriatric Use**

Among 81 patients who received MONJUVI and lenalidomide in L-MIND, 72% were 65 years and older, while 38% were 75 years and older. Clinical studies of MONJUVI did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs compared to that of younger subjects. Patients 65 years and older had more serious adverse reactions (27%) than younger patients (39%).

This is a brief summary of information about MONJUVI. This information is not comprehensive. Visit MONJUVI.com or call (844) 667-1992 to obtain the full Prescribing Information.
Investigators Untangle Emerging Strategies for Gastric Cancer

by BRITTANY LOVELY

FINDINGS FROM CLINICAL TRIALS evaluating HER2-directed and immunotherapeutic approaches for treating patients with gastric cancer are among recent data attracting interest from experts in the gastrointestinal cancer field. The results of 4 studies presented at the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program were the topic of discussion when a panel of specialists got together for The Talk, a new OncLive® video program that features lively exchanges about practical oncology issues in a virtual format.

Moderator Yelena Y. Janjigian, MD, was joined for the roundtable by Jaffer A. Ajani, MD; Daniel Catenacci, MD; and Zev A. Wainberg, MD. The conversation revolved around the results of the following studies:

- RTOG 1010 (NCT01196390), evaluating radiotherapy plus chemotherapy with and without trastuzumab (Herceptin) in HER2-overexpressing esophageal adenocarcinoma. Trastuzumab, a HER2 inhibitor, is approved for HER2-overexpressing metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.1
- DESTINY-Gastric01 (NCT03329690), testing fam-trastuzumab deruxtecan (Enhertu) in previously treated HER2-overexpressing gastric or GEJ adenocarcinoma. In April 2020, the FDA approved trastuzumab deruxtecan, a HER2-directed antibody-drug conjugate, for unresectable or metastatic HER2-positive breast cancer.2,3
- KEYNOTE-061 (NCT02370498), assessing pembrolizumab (Keytruda) versus paclitaxel in advanced gastric or GEJ cancer. Pembrolizumab, a PD-1 immune checkpoint inhibitor, is indicated for patients with recurrent locally advanced metastatic gastric or GEJ tumors that express PD-L1 (combined positive score [CPS] ≥ 1).4
- RAMIRIS (AIO; NCT03081143), investigating ramucirumab (Cyramza) with either FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) or paclitaxel for advanced or metastatic GEJ adenocarcinoma. Ramucirumab, a VEGFR2 inhibitor, is approved for advanced or metastatic gastric or GEJ cancer with disease progression after chemotherapy.5

Janjigian launched the discussion by delving into the RTOG 1010 trial, which attempted unsuccessfully to establish a disease-free survival (DFS) benefit for adding trastuzumab to trimodality treatment.

Janjigian asked:

JANJIGIAN Several important findings presented at ASCO involved targeting HER2 both in the locally advanced and the metastatic setting. Why do you think RTOG 1010 failed [Table 1]? 

CATENACCI I think it was multifactorial: 1 aspect is just an inherent issue with the perioperative studies in this disease. It’s difficult to accrue, and now you’re limiting it to 10% to 15% of the patients who have HER2 amplification. So, inevitably, it’s going to be difficult to accrue to such a study.
The target hazard ratio, I would say, is potentially unrealistic—a hazard ratio of 0.64 DFS. Even in breast cancer, where trastuzumab was used in the adjuvant setting, the hazard ratio for DFS in a positive study was 0.77, in a disease where it works and works better than here. So, I think that to all of a sudden have a [statistically significant] hazard ratio of 0.60 was a little bit unrealistic. But again, that was just a numbers thing, and ultimately, this was a 200-patient study, which is small for a phase 3 study and more like a phase 2 type of study. This was a complicated study; underpowered, perhaps, for what they were trying to achieve and overtly complex in some ways. But I don’t know if this means that adjuvant or perioperative trastuzumab should be abandoned.

AJANI Another thing to consider: I don’t think we need to pursue this group of patients right now, because as everybody said, it takes forever to accrue. But I think a molecule like ZW25 [zanidatamab] or even, you know, DS-8201a [trastuzumab deruxtecan], could have been even more effective with a reduced dose.

JANJIGIAN Do you think there are enough data based on DESTINY-Gastric01 [Table 2.1-3] to consider trastuzumab deruxtecan in the third-line setting patients in the United States or Europe?

WAINBERG I think the study is compelling. It was designed cleverly, in such a way that it allowed patients in Asia to be randomized only to either single-agent irinotecan or paclitaxel, not ramucirumab; they had already progressed on that. I think before we introduce trastuzumab deruxtecan to patients in the United States, we’re going to want to see the ongoing data from this country, or the Western world, I should say.

JANJIGIAN If you have a HER2-positive patient in the third-line setting and you somehow magically have access to trastuzumab deruxtecan, would you give them irinotecan in third line in the United States, as opposed to giving them trastuzumab deruxtecan? You can’t say you’re going to put them on the trial. Let’s say there’s no trial available.

AJANI This is a very active drug. There is no question about it. In the third line, you’re getting a 40% response rate. That doesn’t happen with any other treatment that we know; maybe ZW25 comes close. So that’s really important thing.

But if you look at the toxicity table, in every important category, this drug has more events than chemotherapy does.

CATENACCI I would really echo Dr Wainberg’s point that we need to see the performance of this drug in the Western population, where there is more proximal disease, such as junction esophageal cancer compared with a majority distal...
gastric cancer: different cancers, different biology, different heterogeneity.

To subject our patients in the third-line setting to nivolumab [Opdivo] or pembrolizumab for PD-L1, where the responses are in single digits, or punish them with cytotoxic chemotherapy, when the responses and survival are measured in months, is not an ideal option. I think realistically, there is such a disparity between Asia and the West that we will have to wait another 2 years for data. I’m not suggesting we use trastuzumab deruxtecan in first line or second line. But the truth is, in third line, you really don’t have anything to offer to your patients.

### TABLE 3. Key Findings for Pembrolizumab

<table>
<thead>
<tr>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td><strong>KEYNOTE-061 (NCT02370498):</strong> randomized phase 3 trial assessing pembrolizumab versus paclitaxel in patients with advanced gastric or GEJ cancer who have had tumor progression after first-line treatment with platinum and fluoropyrimidine doublet therapy</td>
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<tr>
<td><strong>Outcomes</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
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<tr>
<td><strong>Pembrolizumab</strong></td>
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<tr>
<td><strong>Oranges</strong></td>
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<tr>
<td><strong>Median OS, months</strong></td>
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<tr>
<td><strong>Median PFS, months</strong></td>
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<tr>
<td><strong>ORR</strong></td>
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<tr>
<td><strong>CR</strong></td>
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<tr>
<td><strong>SD</strong></td>
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<tr>
<td><strong>PD</strong></td>
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</tbody>
</table>

**CPS, combined positive score; CR, complete response; DOR, duration of response; GEJ, gastroesophageal junction; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.**

*a*Response by blind independent central review, RECIST v.1.1 criteria.

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### TABLE 4. Key Findings for Ramucirumab

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAMIRIS (AIO; NCT03081143):</strong> Randomized phase 2/3 study of ramucirumab plus FOLFIRI versus ramucirumab plus paclitaxel in patients with advanced or metastatic gastric cancer who have had tumor progression after first-line treatment with platinum and fluoropyrimidine doublet therapy</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
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<td>---</td>
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<tr>
<td><strong>Oranges</strong></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
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<tr>
<td><strong>ORR in patients pretreated with docetaxel</strong></td>
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<tr>
<td><strong>DCR</strong></td>
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<tr>
<td><strong>DCR in patients pretreated with docetaxel</strong></td>
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<tr>
<td><strong>CR</strong></td>
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<td><strong>PR</strong></td>
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<tr>
<td><strong>SD</strong></td>
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<tr>
<td><strong>PD</strong></td>
</tr>
<tr>
<td><strong>Not evaluable</strong></td>
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<tr>
<td><strong>Median OS, months</strong></td>
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<tr>
<td><strong>Median PFS, months</strong></td>
</tr>
<tr>
<td><strong>Median OS in patients pretreated with docetaxel, months</strong></td>
</tr>
<tr>
<td><strong>Median PFS in patients pretreated with docetaxel, months</strong></td>
</tr>
</tbody>
</table>

**CR, complete response; DCR, disease control rate; FOLFIRI, infuscin, leucovorin, 5 fluorouracil; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.**

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**JANJIGIAN** Are you sort of heartbroken and over targeting HER2 in the neoadjuvant or adjuvant setting? What would you think if you were to design a trial now?

**WAINBERG** For HER2 studies in the adjuvant setting, asking this question a little simpler might be better because of the challenges of enrolling this patient population and also recognizing that trastuzumab is going to be used a lot in the first line and in second line—or not just trastuzumab but also other anti-HER2 agents they’ll be exposed to over the course of their life. So, it’s going to require some degree of change in study design, I think, from the ones that we’ve been using to date.

**JANJIGIAN** I know that there have been strong feelings about approval of pembrolizumab for TMB [tumor mutational burden]–high population. What are your thoughts on the recent tumor-agnostic approval for pembrolizumab?

**WAINBERG** I think the FDA is sending us all a nice message that they like tumor-agnostic approvals, and that’s very clear. And that’s a very interesting and important point to keep in mind as we continue to do new drug development. These tumor-agnostic approvals are here to stay, I think. However, TMB is very confusing, and I would say that there is not still a standard, absolute best way to do this.

We saw at ASCO how, even within the same studies, different measurements of TMB are used, and they’re not absolutely the same. The way the FDA defined it, patients with a TMB of 10 or more [≥ 10 mutations/megabase] are eligible. If I have a patient in the office who has noncolorectal cancer, gastrointestinal, or gastric primary cancer and has a high TMB score, independent of CPS, I think this is something to consider now, whereas before we weren’t checking it. It’ll be interesting to see how quickly this gets adopted, because it’s not necessarily standardized just yet.

**JANJIGIAN** It certainly highlights the importance of NGS [next-generation sequencing] in these diseases.

**WAINBERG** We have to consider the fact that in the community...
practices, the majority of patients aren’t getting NGS testing at this point. So, are clinicians to begin ordering TMB on every single patient just because we have an FDA approval for second line? This is a particularly difficult question to answer, actually.

**JANJIGIAN**

Most referrals that come to me from the community already have Foundation Medicine or 1 of the other commercial platforms done. Is NGS typically available to your patients outside of your academic center?

**CATENACCI**

I’ve noticed, at least in the Chicago area, that over the years—and certainly now with FDA approval of the Foundation One platform and Medicare payments and many other commercial companies offering these assays—the majority of our patients we’re seeing as consults already have it from the local oncologists.

And so, I don’t think that’s going to be a barrier there. Along the points that were mentioned earlier, it was sort of the same question as to when the MSI [microsatellite instability]-high pan tumor approval came out. There was a similar question: Do we have to check all our upper-GI cancers for MSI high? And the answer should be yes. I’m not convinced yet about TMB, and I’d like to see more data after excluding MSI high, which are all TMB high and with high CPS.

Is this still a residual benefit of those other TMB high cancers? I want to see a little bit more information before I jump at that one.

**JANJIGIAN**

Could you discuss the subgroup of KEYNOTE-061 data (Table 3) and the Mayo data suggesting that pembrolizumab may work better in second- or third-line therapy even after pembrolizumab failures? How does that fit into your thoughts on sequencing of immunotherapy once you administer it?

**AJANI**

I think we have seen that phenomenon from very early on, but I don’t think the data are all that convincing at the moment. I’m not aware of this phenomenon in other tumor types where immunotherapy is used up front.

As you mentioned, pembrolizumab is not necessarily a very good drug in gastric cancer because most patients don’t respond, and so we should start selecting those who have high CPS or high TMB, and we’re not doing that.

I think it is fantastic because you’ve got TMB, you’ve got high CPS score, you have algorithms now with NGS that can figure out the neoantigen, whether they’re immunogenic or not. These things are coming our way, and it’s exciting that we will be able to select drugs based on that.

**JANJIGIAN**

Do you use ramucirumab with any other thoughts about AIO [RAMIRIS] data [Table 4] that were presented?

**AJANI**

I think it’s an important study because some people are using taxane up front, which they shouldn’t. Even the FLOT authors’ have recently published, saying, “Don’t do that in the metastatic setting.” A lot of times you have a patient coming off first-line therapy with significant neuropathy, and then you can’t use paclitaxel, so I think this study probably will become important. And I think I agree with the conclusion to conduct a phase 3 study.

**WAINBERG**

Some clinicians use FOLFIRI plus ramucirumab in gastric cancer a lot sooner than we tend to do in the United States. There are already good safety data with this regimen in many cancers, including colorectal cancer and gastric cancer. I think it’s certainly a reasonable option for someone who’s been on platinum-based therapy and a taxane to use this regimen.

It’s an active regimen, but I agree with Dr Ajani—it’s going to be a challenge, and we need to see what the control arm is going to be as they initiate the randomized phase 3 trial.

**JANJIGIAN**

Do we think this is a worthy phase 3 trial to run? It seems like we should be answering more innovative questions.

**CATENACCI**

I completely agree. In my practice, I’ve been using FOLFIRI plus ramucirumab since, essentially, ramucirumab was approved years ago. And in fact, Dr Wainberg and I, and also Dr Sam Klempner, put our data together, and we already did a retrospective analysis. It should be noted that this regimen was added to the NCCN [National Comprehensive Cancer Network] guidelines as an option for second line in January.

So, this is an option. We have now randomized phase 2 data showing it’s at least equivalent, if not trending to better PFS. I agree with you: I don’t think it’s necessary to waste resources on this in the second line. I think it should already be something that is an option for patients. It’s common to have neuropathy after first-line platinum. And what are you going to do? It just makes a lot of sense to use FOLFIRI plus ramucirumab in that setting. So, for me, it’s a no-brainer, and it’s already part of my practice.

**REFERENCES**


THE EVIDENCE TO FIGHT ON with ONIVYDE®

The first and only FDA-approved treatment, in combination with 5-FU/LV, for metastatic pancreatic cancer after gemcitabine-based therapy, proven to extend overall survival (OS)'

INDICATION
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

WARNINGS AND PRECAUTIONS

Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE + 5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE + 5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset ≥24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE + 5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE + 5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE 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 contraception during and for 1 month after ONIVYDE treatment.

ADVERSE REACTIONS

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%, severe 9%, 4%]), fatigue/asthenia (any 56%, 43%, severe 21%, 10%), vomiting (any 52%, 26%,...
ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST-GEMCITABINE METASTATIC PANCREATIC CANCER**

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic pancreatic cancer.

* Liposomal irinotecan + 5-FU/LV is the only Category 1 National Comprehensive Cancer Network® (NCCN®) chemotherapy recommendation for patients with post-gemcitabine metastatic pancreatic cancer with good performance status and disease progression. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

1 NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m² every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were progression-free survival and objective response rate.1,4

FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE1

- Proven in combination with 5-FU/LV in NAPOLI-1—the largest phase 3 trial in patients with metastatic pancreatic cancer with disease progression after gemcitabine-based therapy.1,4

ADVERSE REACTIONS

The most common serious adverse reactions (≥2%) of ONIVYDE were neutropenic fever/neutropenic sepsis, neutropenia, diarrhea, and dehydration (4%, 2%).

- Of less common (<20%) adverse reactions, patients receiving ONIVYDE + 5-FU/LV who experienced Grade 3/4 adverse reactions at a ≥2% higher incidence of Grade 3/4 toxicity vs the 5-FU/LV arm, respectively, were sepsis (3%, 1%), neutropenic fever/neutropenic sepsis (3%, 0%), gastroenteritis (3%, 0%), intravenous catheter-related infection (3%, 0%), weight loss (2%, 0%), and hypokalemia and dehydration (4%, 2%).

- The laboratory abnormalities in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence vs the 5-FU/LV arm were anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%), increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%), hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypercalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%), increased creatinine (any 18%, 13%; severe 0%, 0%).

- ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. Grade 1/2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients.

- Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE + 5-FU/LV.

- The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.


DRUG INTERACTIONS

Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme-inducing therapies 22 weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 orUGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy and Reproductive Potential

Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

Lactation

Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

Pediatric

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

DOSAGE AND ADMINISTRATION

The recommended dose of ONIVYDE is 70 mg/m² intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD.

Do not substitute ONIVYDE for other drugs containing irinotecan HCl.


For more information, visit ONIVYDEinfo.com
ONIVYDE® (irinotecan liposome injection) for intravenous use

Initial U.S. Approval: 1996

BRIEF SUMMARY: refer to full Prescribing Information for complete product information.

1. INDICATIONS AND USAGE

ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas following gemcitabine-based therapy.

2. DOSAGE AND ADMINISTRATION

Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce periodically during treatment. (see Dosage and Administration, 2.2)

3. ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label. The most common adverse reactions occurring in ≥20% of patients receiving ONIVYDE®/5-FU/LV are: diarrhea, fatigue, nausea, and vomiting. Other reactions include: neutropenia, rash, skin rash, pyrexia, and stomatitis.

4. CONTRAINDICATIONS

ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

5. WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia: ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and in 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosage and Administration, 2.2).

5.2 Severe Diarrhea: ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction. Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) (see Cholinergic Reactions, 6.1).

An individual patient may experience both early- and late-onset diarrhea. In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose (see Dosage and Administration, 2.2).

5.3 Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1).

6. ADVERSE REACTIONS

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

- Severe Neutropenia (see Warnings and Precautions, 5.1: Boxed Warning)
- Severe Diarrhea (see Warnings and Precautions, 5.2: Boxed Warning)
- Interstitial Lung Disease (see Warnings and Precautions, 5.3)
- Severe Hypersensitivity Reactions (see Warnings and Precautions, 5.4)

6.1 Clinical Trials Experience

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specific therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specific therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² every 46 hours every 2 weeks (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² every 24 hours for 4 weeks followed by 2 week rest (5-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/5-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue, asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥20%, Grade 3 or 4) were lymphopenia and neutropenia. The most common severe adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Do not administer ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

The following laboratory abnormalities were reported (NCI CTCAE v4.0) with higher incidence (≥5% difference for Grades 1–4 or ≥2% difference for Grades 3–4) in the ONIVYDE®/5-FU/LV Arm:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE®/5-FU/LV n=117</th>
<th>5-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea†</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic infection/febrile neutropenia sepsis</td>
<td>h</td>
<td>3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Intravenous catheter-related infection</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions:

- Fatigue/asthenia | 56 | 21 | 43 | 10 |
- Pyrexia | 23 | 2 | 11 | 1 |

Metabolism and nutrition disorders:

- Decreased appetite | 44 | 4 | 32 | 2 |
- Weight loss | 17 | 2 | 7 | 0 |
- Dehydration | 8 | 4 | 7 | 2 |

Skin and subcutaneous tissue disorders:

- Alopecia | 14 | 1 | 5 | 0 |

*NCI CTCAE v4.0.
†Early diarrhea: onset ≤24 hours of ONIVYDE® administration.
‡Late diarrhea: onset >1 day after ONIVYDE® administration.
§Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.

Cholinergic Reactions: ONIVYDE® can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diarrhea, and pharyngitis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE®-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea. Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritis, occurring on the day of ONIVYDE® administration, were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV. The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥2% difference Grades 3–4 [severe]) according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/5-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. Hematologic: anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). Hepatic: increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%). Metabolic: hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hypernatremia (any 27%, 12%; severe 5%, 3%). Renal: increased creatinine (any 18%, 13%; severe 0%, 0%).

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

7.2 Strong CYP3A4 or UGT1A1 Inhibitors: Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE® with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy, Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

8.2 Lactation, Risk Summary: There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk (see Data in the full Prescribing Information). Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE®, advise a nursing woman not to breastfeed during treatment with ONIVYDE® and for 1 month after the final dose.

8.3 Females and Males of Reproductive Potential, Contraception, Females: ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations, 8.1). Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month after the final dose. Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE® and for 4 months after the final dose (see Nonclinical Toxicology, 13.1).

8.4 Pediatric Use: Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

8.5 Geriatric Use: Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/5-FU/LV in Study 1, 49% were ≥65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdose of ONIVYDE®.
IMPLEMENTING POPULATION-BASED BRCA1/2 testing is not only cost-effective in high- and upper middle-income countries but could also prevent tens of thousands of breast and ovarian cancer cases compared with the current clinical strategy, which recommends testing only for high-risk women, according to new data from an international study.

Investigators of the research effort, led by Queen Mary University of London in England, sought to compare the cost-effectiveness and preventive impact of BRCA testing in a broader population versus standard testing practice in countries considered high-income (HIC), including the United Kingdom (UK), United States (US), and Netherlands; upper middle-income (UMIC), China and Brazil; and low middle-income (LMIC), India. Investigators conducted separate analyses for population-based BRCA screening in HIC, UMIC, and LMIC using payer and societal perspectives and compared the cost-effectiveness and health impact of this testing format with that of clinical criteria/family history-based testing.

Findings indicated that population-based testing, which would entail offering all women 30 years and older BRCA1/2 testing and classifying them as BRCA-positive or BRCA-negative, was “highly cost-effective” in HIC and UMIC from a payer perspective. In the UK, US, and Netherlands, the incremental cost-effectiveness ratio (ICER) was $21,191 per quality-adjusted life year (QALY), $16,552 per QALY, and $25,215 per QALY, respectively. This population-based approach was deemed cost-effective in UMIC, where the ICER for China was estimated at $23,485 per QALY and at $20,995 per QALY for Brazil. The proposed strategy for BRCA testing was not cost-effective in LMIC (India ICER, $32,217/QALY; TABLE).

To be cost-effective in LMIC such as India from a societal perspective, BRCA testing would need to decrease to approximately $172 per test (ICER, $19,685/QALY). Further, the expenses relative to BRCA testing would qualify as cost-effective in India if they fell to $95 per test (ICER, $19,670/QALY).

When evaluated in the context of local, country-specific guidelines, population-based BRCA testing was cost-effective from a payer standpoint: It saved the UK £24,066, based on an ICER per QALY; the US $16,552 (ICER/QALY); and the Netherlands $17,655 (ICER/QALY). It was also cost-saving from a societal perspective, translating to savings of $3,543 in the UK (ICER/QALY, $4,018 in the US (ICER/QALY), and $3,185 in the Netherlands (ICER/QALY).

STUDY METHODS
In this study, the payer perspective was limited to the expenses associated with the health care system, including the costs of genetic testing, screening, and prevention. Although some countries only take the payer perspective into account, “a societal perspective is recommended by the World Health Organization and other international bodies,” the authors wrote. A societal perspective analysis is associated with a lower ICER per QALY than a payer perspective because it incorporates additional costs connected to productivity loss. For example, the societal standpoint would include the loss of income from a patient’s inability to work whereas the payer perspective would not.

Investigators modeled the costs associated with BRCA1/2 testing versus family history-based testing over an individual’s lifetime using the Markov cycles, which depend on life expectancy starting at 30 years, and differ by country. The corresponding Markov cycles for the UK, US, Netherlands, China, Brazil, and India were 53, 52, 53, 48, 49, and 38, respectively.

Markov model outcomes included breast
cancer, ovarian cancer, and the excess deaths prevented by coronary heart disease (CHD). The lifetime costs and QALYs were estimated with population testing and family history testing, and the ICER was calculated by dividing the difference in cost by the difference in health effects between these 2 testing methodologies.

**LIFETIME POPULATION IMPACT**

To assess the lifetime population impact of population-based BRCA screening, investigators evaluated the reduction in breast and ovarian cancer cases and deaths, as well as excess deaths from CHD, that would result from the implementation of broader-scale testing. Two of the preventive options afforded to BRCA-mutation carriers include risk-reducing mastectomy and risk-reducing salpingo-oophorectomy. All women undergoing risk-reducing salpingo-oophorectomy have an increased risk of fatal CHD, hence the investigators’ choice to evaluate this outcome.

Regarding the diagnoses that could be spared with population-based BRCA testing, investigators found that 2319 to 2666 breast cancer and 327 to 449 ovarian cancer cases could be prevented per million-women. Stratified by country, this population-based approach could prevent an additional 57,708 breast cancer cases in the UK; 269,089 in the US; 15,181 in the Netherlands; 1,050,314 in China; 156,299 in Brazil; and 692,571 in India. It would spare a corresponding 9727; 43,817; 2,557; 154,756; 25,170; and 97,659 ovarian cancer cases, respectively. Investigators added that the benefit may be even greater than these data project due to the “huge underutilization of BRCA testing, along with limited access and uptake associated with current treatment pathways,” which could lead to an underestimation of the cases that could potentially be prevented with this broader approach.

**BRCA TESTING IS UNDERUTILIZED**

Inherited BRCA1/2 mutations drive about 10% to 20% of ovarian cancer cases and 6% of breast cancer diagnoses. Women who harbor BRCA1/2 mutations have a 17% to 44% risk and a 69% to 72% risk of developing ovarian cancer and breast cancer, respectively.

Although those in the oncology field recognize the prognostic implications of BRCA1/2 alterations and their actionability, globally, clinical guidelines only support genetic testing for high-risk women who meet certain criteria, such as having a strong family history of breast or ovarian cancer, and testing nevertheless remains underutilized. For example, more than 50% of BRCA-mutation carriers do not meet the clinical criteria to qualify for testing, and only 20% of eligible women in the United States have undergone genomic screening. Additionally, in the United Kingdom, more than 97% of BRCA1/2-mutation carriers have not been identified.

These clinical realities, coupled with findings from the study, support a paradigm shift toward population-based BRCA testing to maximize breast and ovarian cancer prevention, the authors concluded.

**REFERENCE**


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**TABLE.** Population-Based Testing Versus Family History-Based Testing: Cost Savings From the Payer Perspective**a,b**

<table>
<thead>
<tr>
<th>Country</th>
<th>Population-based testing</th>
<th>Family history-based testing</th>
<th>ICER, Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost</td>
<td>Cost</td>
<td>Cost/QALY</td>
</tr>
<tr>
<td>UK</td>
<td>$2543</td>
<td>$2336</td>
<td>$21,191</td>
</tr>
<tr>
<td>US</td>
<td>$7250</td>
<td>$7122</td>
<td>$16,552</td>
</tr>
<tr>
<td>Netherlands</td>
<td>$2478</td>
<td>$2239</td>
<td>$25,215</td>
</tr>
<tr>
<td>China</td>
<td>$820</td>
<td>$665</td>
<td>$23,485</td>
</tr>
<tr>
<td>Brazil</td>
<td>$834</td>
<td>$586</td>
<td>$20,995</td>
</tr>
<tr>
<td>India</td>
<td>$463</td>
<td>$369</td>
<td>$32,217</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

**a**All costs are reported at 2016 US dollars, converted by purchasing-power-parity factor, which reflects the value of a country’s currency required to purchase the equivalent amounts of goods/services in the domestic market as the US dollar would buy in the United States.

**b**The payer position includes the expenses associated with the healthcare system, including the costs of genetic testing, screening, and prevention.

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High-income country  Upper middle-income country  Low middle-income country

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**First of Its Kind MMRF CureCloud Makes Way for Precision Medicine in Myeloma**

Hearn Jay Cho, MD, PhD, an associate professor of medicine of Hematology and Medical Oncology at the Icahn School of Medicine at Mount Sinai Hospital and the chief medical officer of the Multiple Myeloma Research Foundation, and Irene Ghobrial, MD, a professor of medicine at Harvard Medical School and director of the Clinical Investigator Research Program at Dana-Farber Cancer Institute, discuss the inspiration for the MMRF CureCloud, how it advances precision medicine, and the long-term goals of the study for patients and physicians alike.


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**Marvels in Medicine: Dr Gradishar on His Pursuit of Precision Medicine in Breast Cancer**

In an exclusive interview, William J. Gradishar, MD, chief of hematology and oncology in the Department of Medicine, Betsy Bransom Professorship of Breast Oncology, and professor of medicine in Hematology and Oncology at Northwestern University’s Feinberg School of Medicine, shares the path that led him to specialize in the field of breast cancer, collective experiences that have inspired him throughout his career, and his hope for the continued transition from “shotgun medicine” to precision medicine in the field.

In adults with polycythemia vera (PV) who have had an inadequate response to hydroxyurea (HU)³

**INTERVENe WITH JAKAFI®**

**TO ACHIEVE DURABLE COUNT CONTROL**

In the phase 3 RESPONSE* trial, Jakafi demonstrated superior results† vs BAT‡

**Composite primary endpoint**

23% (25/110) of patients receiving Jakafi achieved Hct control and ≥35% spleen volume reduction at week 32

VS <1% (1/112) of patients receiving BAT (P < 0.0001)†

* Jakafi 95% CI, 0.15-0.32; BAT 95% CI, 0.00-0.05.

† The composite primary endpoint was defined as Hct control without phlebotomy eligibility and ≥35% spleen volume reduction as measured by CT or MRI.

‡ BAT, best available therapy; CI, confidence interval; Hct, hematocrit; MF, myelofibrosis.

In the phase 3 RESPONSE* trial, all patients were required to demonstrate Hct control between 40% and 45% prior to randomization. After week 32, patients were able to cross over to Jakafi treatment.1,4

**Probability of Maintaining the Primary Response at 5 Years**²

74%

Kaplan-Meier analysis was conducted in week 32 primary responders, beginning at week 32²

Progression was defined as: the first of 2 consecutive Hct assessments that confirmed phlebotomy eligibility, spleen volume assessment that was reduced by <35% from the baseline and that was ≥25% increased at the time of the best-documented spleen volume response, death, or development of MF or acute leukemia³

The median duration of primary response was not reached.


**Indications and Usage**

Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

**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 × 10⁹/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
**In the phase 3 RESPONSE trial,**

**More patients achieved Hct control with Jakafi in the absence of phlebotomy eligibility**

**Individual component of the primary endpoint**

60% (66/110) of patients receiving Jakafi achieved Hct control at week 32

VS 19% (21/112) of patients receiving BAT

- To achieve the Hct control endpoint, patients could not become eligible for phlebotomy between weeks 8 and 32. Phlebotomy eligibility was defined as hematocrit >45% that is ≥3 percentage points higher than baseline or Hct >48% (lower value).

**Probability of Maintaining Hct Control at 5 Years**

- Kaplan-Meier analysis was conducted in week 32 Hct control responders, beginning at week 32
- Progression events for the evaluation of duration of absence of phlebotomy eligibility included first of 2 consecutive Hct assessments that confirms phlebotomy eligibility, death, or development of MF or acute leukemia

(25/110) of patients receiving Jakafi demonstrated superior results vs BAT (21/112) of patients receiving BAT ($p < 0.0001$)

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

**References:**


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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 VeraJakafi is indicated for treatment of polycythemia vera (PV) in adults who have an inadequate response to or are intolerant of hydroxyurea. Acute Graft-Versus-Host Disease Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [See Dosage and Administration (2.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery [see Adverse Reactions (6.4) in Full Prescribing Information]. Perform a pre-treatment complete blood count (CBC) and monitor CBC every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2), and Adverse Reactions (6.4) 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 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 (6.2) in Full Prescribing Information]. 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 patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. More than one of these occurrences or discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [see Dosage and Administration (2.6) in Full Prescribing Information], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. Non-Melanoma Skin Cancer Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. Lipid Elevations Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. ADEVIATIONS No clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [see Warnings and Precautions (5.1) in Full Prescribing Information] • Risk of Infection [see Warnings and Precautions (5.2) in Full Prescribing Information] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see Warnings and Precautions (5.3) in Full Prescribing Information] • Non-Melanoma Skin Cancer [see Warnings and Precautions (5.4) in Full Prescribing Information]. Clinical Trials Experience in Myelofibrosis Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range, 2 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25%, respectively, required a dose reduction before the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi. Jakafi is the double-blind, placebo-controlled study during randomized treatment. Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=155)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
</tr>
<tr>
<td>Bruising a</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dizziness b</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infections c</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Weight Gain d</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster e</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
b Includes confusion, encephalopathy, amnesia, headache and seizures.
c Includes urinary tract infection.
d Includes weight gain.
e Includes herpes zoster.

Table 2: Myelofibrosis: Worsening Hematologic Laboratory Abnormalities in the Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=115)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>96</td>
<td>34</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

a Present values are worst Grade values regardless of baseline.
b 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 7.5% 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 <1% 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 Polycythemia Vera In a randomized, open-label, active-controlled study, 110 patients with PV resistant or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [see Clinical Studies (4.2) in Full Prescribing Information]. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=110)</th>
<th>Placebo (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness b</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia c</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster e</td>
<td>6</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 3 continued above.
Infection chronic HBV infection should be treated and monitored according to clinical guidelines. Advise patients about early signs and symptoms of herpes zoster and to prompt medical care. Prior to initiating Jakafi, patients should be evaluated for latent infection. Risk factors include, but are not limited to, prior active serious infections have resolved. Observe patients receiving Jakafi for 9.5 months (range 0.5 to 17 months), with 89% of patients discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of 6% of patients treated with Jakafi for acute GVHD failing treatment with placebo developed newly occurring or worsening skin lesions (90% vs. 70%). In patients with acute GVHD, reduce Jakafi dose as recommended only when coadministered with ketoconazole, and monitor blood counts more frequently for toxicity and adjust the dose if necessary. The median time to recovery of platelet counts greater than 200 × 10⁹/L was 32 days (range, 2 to 21 years) and included 18 children (age 2 to <12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, and 30 mg/m² twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, were 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults.

Juvenile Animal Toxicity Data Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures (e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis) occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

Geriatric Use Of the total number of patients in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with acute GVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Renal Impairment Total exposure of ruxolitinib and its active metabolites increased with moderate (Clcr 30 mL/min to 59 mL/min) and severe (Clcr 15 mL/min to 29 mL/min) renal impairment, and ESRD on dialysis (see Clinical Pharmacology (12.3) in Full Prescribing Information). Reduce Jakafi dose as recommended (see Dosage and Administration (2.5) in Full Prescribing Information). Hepatic Impairment Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment (see Clinical Pharmacology (12.3) in Full Prescribing Information). Reduce Jakafi dose as recommended (see Dosage and Administration (2.5) in Full Prescribing Information).

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression, including leukopenia, anemia, and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.

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Interest Builds for Targeting TIGIT Checkpoint

by JANE DE LARTIGUE, PhD

TIGIT, AN INHIBITORY IMMUNE checkpoint that plays a central role in limiting antitumor responses, is attracting robust interest in the research community as a novel target for combination therapies across a range of cancer types, particularly solid tumors.

Clinical trials of antibodies directed at TIGIT were initiated several years ago, but until recently little progress appeared to have been made. In March 2020, Roche launched a pivotal phase 3 trial (SKYSCRAPER-01; NCT04294810) evaluating tiragolumab (RG6058), a monoclonal antibody that binds to TIGIT, as frontline therapy for patients with locally advanced unresectable or metastatic non–small cell lung cancer (NSCLC) in combination with the PD-L1 inhibitor atezolizumab (Tecentriq).

Other pharmaceutical developers also joined the race. Most of the novel agents are being paired with immune checkpoint inhibitors (ICIs) in early-phase clinical studies, typically in combination with established and emerging PD-1/PD-L1 pathway ICIs (TABLE, page 78).

The search for alternative immune checkpoints that may offer improved or complementary targets for immunotherapy is aimed at overcoming some of the challenges of ICIs. Despite the transformative success of ICIs in numerous cancer types over the past decade, a substantial proportion of patients do not respond, some immunologically “cold” tumor types are notoriously resistant, and many patients experience severe immune-related adverse events (irAEs).1,2

Although some high-profile disappointments have tempered enthusiasm for novel ICI targets,3,5 the current spate of activity surrounding TIGIT shows that the hunt is still on. Studies combining TIGIT-directed antibodies with PD-1/PD-L1 pathway ICIs have become particularly attractive in light of data showing coexpression of TIGIT and PD-L1 across many types of cancer.6-8

SEVERAL MECHANISMS OF ACTION
Activating and inhibitory receptors on the surface of immune cells, dubbed immune checkpoints, are essential for maintaining a delicate balance between immune response and tolerance. Best known are PD-1 and CTLA-4, coinhibitory receptors that transmit a secondary signal to T cells after antigen priming, which inhibits T-cell activation.1,2

First described in 2009,9 TIGIT is an inhibitory receptor that competes with an activating receptor—in this case DNAM-1, also known as CD226, for binding to the same set of ligands; namely, CD155 and CD112. Regulation of TIGIT activity is made more complex, however, by the fact that it also binds to 2 additional ligands: CD113,6,7,10,11 and, most recently discovered, nectin-4 (FIGURE11).12

These ligands and receptors belong to the nectin/nectin-like family of proteins, a subfamily within the broader immunoglobulin superfamily; CD155 is alternatively known as nectin-like 5; CD112, nectin-2, and CD113, nectin-3. Many members of the family also serve as receptors for viruses, such as the poliovirus; hence, alternative nomenclature for CD155 is the poliovirus receptor (PVR), and CD112, CD113, and nectin-4 are otherwise referred to as PVRL2, PVRL3, and PVRL4, respectively.6,7,10,11

Adding to the complexity, in addition to competing with DNAM-1, TIGIT also competes with 2 inhibitory receptors, CD96 (also known as TACTILE) and CD112R (or PVRIG for PVR related immunoglobulin domain containing) for binding to their respective ligands, CD155 and CD112.6,7,10,11

TIGIT’s predominant ligand is CD155 and, in a hierarchy of binding, it has the highest

FIGURE. TIGIT’s Role in Suppressing Immune Reactions11

The activity of TIGIT, an inhibitory immune receptor, is regulated through a complex set of interactions with ligands and receptors. The illustration depicts immunosuppressive functions involving TIGIT-positive Tregs and CD8-positive T cells and NK cells.

APCs, antigen-presenting cells; NK, natural killer; PVR, poliovirus receptor; Th2, T helper type 2; Treg, regulatory T cell.

TIGIT antibodies.\textsuperscript{15,16} Studies of vibostolimab (MK-7684) and etigilimab (formerly called MTIG7192A) were presented from phase 1 of Cancer (SITC) Annual Meeting, preliminarily favoring immune suppression when TIGIT is expressed.\textsuperscript{5,7,10,11} TIGIT is composed of an extracellular immunoglobulin variable domain, a transmembrane domain, and a short intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM). It is expressed predominantly on natural killer (NK) cells and T cells, major effectors of the immune response.\textsuperscript{5,7,10,11} Upon ligand binding, TIGIT delivers an inhibitory signal into the cell via its ITIM and deactivates an array of downstream cellular proteins that dampen the cell via its ITIM and deactivates an array of downstream cellular proteins that dampen the cell.

EARLY TIGIT FINDINGS

**Vibostolimab**

For several years, a number of pharmaceutical companies have been developing antagonistic antibodies targeting TIGIT. At the 2018 Society for the Immunotherapy of Cancer (SITC) Annual Meeting, preliminary results were presented from phase 1 studies of vibostolimab (MK-7684) and etigilimab (OMP-313M32), both humanized TIGIT antibodies.\textsuperscript{15,16}

In a first-in-human study (NCT02964013), patients with metastatic, previously treated solid tumors were treated with escalating doses (2.1, 7, 21, 70, 210, and 700 mg q3w) of vibostolimab as monotherapy and combined with the PD-1 inhibitor pembrolizumab (Keytruda). Findings were reported for 34 patients treated with monotherapy and 43 who received the combination, which included 13 patients who crossed over from the monotherapy arm.

The overall response rate (ORR) with vibostolimab alone was 3%, including 1 partial response (PR) and 11 patients with stable disease (SD) for a disease control rate (DCR) of 35% (95% CI, 20%-54%). For the combination, the ORR was 19%, including 8 PRs and 12 SDs for a DCR of 47% (95% CI, 31%-62%).\textsuperscript{15}

There were no dose-limiting toxicities (DLTs) and treatment-related adverse events (TRAEs) occurred in 53% (monotherapy) and 65% (combination therapy) of patients, which were grade 3 or higher in 6% and 12% of patients, respectively. The most common TRAEs were fatigue and pruritus in the monotherapy arm and pruritus and rash with combination therapy.\textsuperscript{15}

Merck has started a phase 2 trial testing vibostolimab plus chemotherapy in patients with previously untreated NSCLC (NCT04165070) and has initiated several earlier-phase studies in melanoma and other advanced solid tumors.

**Etigilimab**

Etigilimab was evaluated as a single agent and in combination with the PD-1 antibody nivolumab (Opdivo) in patients with advanced or metastatic solid tumors in a phase 1a study (NCT03119428). Data from 18 patients treated with monotherapy doses ranging from 0.3 to 20.0 mg/kg every 2 weeks, in the dose-escalation portion of the study, demonstrated best response of SD in 7 patients. The agent was well tolerated, with no DLTs, and common TRAEs included rash, fatigue, nausea, pruritus, and cough. Rash, pruritus, autoimmune hepatitis, and stomatitis were among the irAEs.\textsuperscript{16}

The trial was terminated for undisclosed reasons, according to an update posted in August 2020 on ClinicalTrials.gov. However, Mereo BioPharma Group plc, which acquired etigilimab through a merger and has since secured worldwide development rights, plans to launch a phase 1b trial in solid tumors during 2020.\textsuperscript{17}

**SETTING THE PACE: TIRAGOLUMAB**

Early clinical experience highlighted limited efficacy of TIGIT antibodies as monotherapy and ongoing trials focus on combinations, particularly in light of preclinical evidence of synergy with PD-1 inhibition.\textsuperscript{18}

Tiragolumab (formerly called MTIG7192A) is a fully human monoclonal antibody that blocks the binding of TIGIT to its PVR and CD226 ligands; it has emerged as the current frontrunner.\textsuperscript{19,20} In the first-in-human phase 1 G030103 study (NCT02794571), the results of which were presented at the American Association for Cancer Research Virtual Annual Meeting II, tiragolumab was evaluated as monotherapy and in combination with atezolizumab in advanced solid cancers.

In the trial’s dose-escalation portion, 24 patients were treated with monotherapy and 49 with combination therapy. There were no objective responses with tiragolumab monotherapy, although 4 patients showed tumor reduction. With the combination, 10 patients showed tumor reduction, including 5 PRs. In an expansion cohort, 13 immunotherapy-naïve patients with PD-L1-positive NSCLC (≥ 1%) were treated with combination therapy. Six patients (46%) responded, including 2 who experienced a CR and 4 reaching PRs, for a DCR rate of 85%.\textsuperscript{21}

Tiragolumab was well tolerated and had an acceptable safety profile across all doses studied. There were no DLTs, with just 4% grade 3 or higher TRAEs in both arms and no grade 5 events. The most common AEs included anemia, constipation, and fatigue. Overall, 17% of those who received tiragolumab monotherapy and 59% who had the combination experienced irAEs.\textsuperscript{21}

Building upon these results, the phase 2 CITYSCAPE trial (G040290; NCT03563716) was initiated to compare tiragolumab (600 mg q3w) plus atezolizumab with atezolizumab plus placebo in patients with newly diagnosed, PD-L1-positive (tumor proportion score [TPS] ≥ 1% of tumor cells) NSCLC, without EGFR or ALK alterations.\textsuperscript{19}

In an updated analysis, both ORR and median PFS were improved in the tiragolumab arm, according to findings...
presented at the 2020 American Society for Clinical Oncology Virtual Scientific Program. Over a median follow-up of 10.9 months, the ORR in the intention-to-treat population (N = 135) was 37% in the tiragolumab arm compared with 21% with atezolizumab alone. The median PFS was 5.55 months (95% CI, 4.21-10.4) versus 3.88 months (95% CI, 2.73-4.53), for a stratified HR favoring the combination of 0.58 (95% CI, 0.38-0.89).¹⁹

In an exploratory analysis, the ORR in the cohort of patients (n = 58) with high PD-L1 expression (TPS ≥ 50%) was 66% for the tiragolumab combination versus 24% with atezolizumab alone. The median PFS was not reached (NR) for the combination (95% CI, 5.49 months-NR) compared with 4.11 months (95% CI, 2.07-4.73) for atezolizumab (unstratified HR, 0.30; 95% CI, 0.15-0.61).¹⁹

The combination was well tolerated, with similar rates of overall and grade 3 or higher any-cause AEs in the 2 arms. The incidence of irAEs was higher with the combination, although these primarily involved rash and infusion-related reactions and were of grade 1 or 2 severity.¹⁹

Roche has launched an extensive development program involving tiragolumab, including pivotal phase 3 clinical trials in NSCLC (SKYSCRAPER-01; NCT04294810) and extensive-stage small cell lung cancer (SKYSCRAPER-02; NCT04256421).

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**TABLE. TIGIT-Directed Agents in Clinical Development**

<table>
<thead>
<tr>
<th>Drug/Industry sponsor(s)</th>
<th>Ongoing clinical trials (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tiragolumab</strong> (MTIG7192A/RG6058) Roche/Genentech</td>
<td><strong>Phase 3</strong>&lt;br&gt;- With atezolizumab in previously untreated locally advanced, unresectable/metastatic PD-L1+ NSCLC (SKYSCRAPER-01; NCT04294810)&lt;br&gt;- With atezolizumab + chemotherapy in previously untreated ES-SCLC (SKYSCRAPER-02; NCT04256421)&lt;br&gt;<strong>Phase 2</strong>&lt;br&gt;- With atezolizumab in metastatic and/or recurrent PD-L1+ cervical cancer (SKYSCRAPER-04; NCT04300647)&lt;br&gt;- With atezolizumab in chemotherapy-naïve, locally advanced/metastatic NSCLC (CITYSCAPE; NCT03963716)*&lt;br&gt;<strong>Phase 1/2</strong>&lt;br&gt;- With atezolizumab +/- chemotherapy in locally advanced, unresectable or metastatic gastric/GEJ/esophageal cancer (MORPHEUS-Gastric and Esophageal Cancer; NCT03281369)&lt;br&gt;- With atezolizumab in locally advanced/metastatic urothelial carcinoma after failure of platinum-based chemotherapy (MORPHEUS mUC; NCT03869190)&lt;br&gt;- With atezolizumab + chemotherapy in metastatic PDAC (MORPHEUS-Pancreatic Cancer; NCT03191390)&lt;br&gt;<strong>Phase 1</strong>&lt;br&gt;- With or without daratumumab or rituximab in relapsed/refractory multiple myeloma or NHL (NCT04045028)&lt;br&gt;- With or without atezolizumab +/- chemotherapy in locally advanced/metastatic tumors (NCT02794571)</td>
</tr>
<tr>
<td><strong>Domvanalimab</strong> (AB154) Arcus Biosciences</td>
<td><strong>Phase 2</strong>&lt;br&gt;- With zimberelimab (PD-1 mAb) in previously untreated, PD-L1+, locally advanced or metastatic NSCLC (ARC-7; NCT04262856)&lt;br&gt;<strong>Phase 1</strong>&lt;br&gt;- With or without zimberelimab in advanced solid malignancies (NCT03628677)</td>
</tr>
<tr>
<td><strong>Vibostolimab</strong> (MK-7684) Merck</td>
<td><strong>Phase 2</strong>&lt;br&gt;- With pembrolizumab in chemotherapy in previously untreated advanced NSCLC (KEYNOTE-01A; NCT04165070)&lt;br&gt;<strong>Phase 1/2</strong>&lt;br&gt;- With pembrolizumab in patients with anti-PD-1/PD-L1 refractory advanced melanoma (NCT04305041)&lt;br&gt;- With pembrolizumab in previously untreated advanced melanoma (NCT04305054)&lt;br&gt;- With pembrolizumab as neoadjuvant therapy in stage III melanoma (NCT04303169)&lt;br&gt;<strong>Phase 1</strong>&lt;br&gt;- With or without pembrolizumab in advanced solid tumors (NCT02964013)*</td>
</tr>
<tr>
<td><strong>BMS-986207</strong> Bristol Myers Squibb</td>
<td><strong>Phase 1/2</strong>&lt;br&gt;- With or without pomalidomide and dexamethasone in relapsed/refractory multiple myeloma (NCT04150965)&lt;br&gt;- With or without nivolumab in advanced/metastatic solid tumors (NCT02913313)*</td>
</tr>
<tr>
<td><strong>COM902</strong> Compugen</td>
<td><strong>Phase 1</strong>&lt;br&gt;- In advanced malignancies (NCT04354246)</td>
</tr>
<tr>
<td><strong>BGB-A1217</strong> BeGene</td>
<td><strong>Phase 1</strong>&lt;br&gt;- With tirapazolizumab (PD-1 mAb) in advanced solid tumors (NCT04047862)</td>
</tr>
<tr>
<td><strong>ASP8374</strong> Astellas Pharma</td>
<td><strong>Phase 1</strong>&lt;br&gt;- With or without pembrolizumab in advanced solid tumors (NCT03260322)</td>
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<tr>
<td><strong>IBI939</strong> Innovent Biologics</td>
<td><strong>Phase 1</strong>&lt;br&gt;- With or without sintilimab (PD-1 mAb) in advanced malignancies (NCT04353830)</td>
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<tr>
<td><strong>EOS-448</strong> iTeos Therapeutics</td>
<td><strong>Phase 1/2</strong>&lt;br&gt;- In advanced cancers (NCT04335253)</td>
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<td><strong>M6223</strong> EMD Serono/Merck</td>
<td><strong>Phase 1</strong>&lt;br&gt;- With or without binutrafusp alfa (TGF-β/PD-L1 fusion protein) in metastatic/locally advanced unresectable solid tumors (NCT04457778)</td>
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ES-SCLC, extensive stage small cell lung cancer; GEJ, gastroesophageal junction; mAb, monoclonal antibody; mUC, metastatic urothelial carcinoma; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; TGF-β, transforming growth factor beta.

*Study is active but not recruiting participants.
DESpite the improved outcomes seen with HER2-targeted therapies in patients with breast cancer in both the early and advanced settings, almost all patients with metastatic HER2-positive breast cancer eventually progress on anti-HER2 therapy because of de novo or acquired resistance.¹,² This has prompted efforts to improve anti-HER2 treatment strategies, and several new agents recently have been approved by the FDA. As the armamentarium of novel therapies expands, so does the need for an understanding of safety and efficacy in patients, especially those with brain metastases.

During an OncLive Peer Exchange®, a panel of breast cancer experts discussed a variety of new and emerging agents to treat patients with advanced or metastatic HER2-positive breast cancer with disease progression following treatment with at least 1 anti-HER2 therapy, including the recent approvals of a new antibody-drug conjugate, several novel tyrosine kinase inhibitors (TKIs), and a new anti-HER2 antibody. “The HER2-positive space is really the most exciting space right now in terms of what we can do or will be able to do in the clinic very soon to offer yet more life-prolonging therapies [to our patients],” Priyanka Sharma, MD, said.

TRASTUZUMAB DERUXTECAN
Fam-trastuzumab deruxtecan-nxki (Enhertu) is an antibody-drug conjugate that has shown remarkable results in treating unresectable or metastatic HER2-positive breast cancer. “The payload with this drug is a TOPO1 [type I topoisomerase] inhibitor, and there is a high drug-to-antibody ratio. There is also some bystander effect with it easily crossing the cell membrane. It has a relatively short half-life, so the thought is that it can get to neighboring cells but doesn’t hang around for very long,” Claudine J. Isaacs, MD, said.

On December 20, 2019, based on data from the phase 2 DESTINY-Breast01 trial (NCT03248492), the FDA granted accelerated approval to trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer who received at least 2 prior anti-HER2–based regimens in the metastatic setting.³ The study reported an objective response rate (ORR) of 60.3%, which was particularly remarkable because patients in the study were heavily pretreated, with a median of 6 prior treatments (range, 2-27), including trastuzumab (Herceptin; 100%), ado-trastuzumab emtansine (T-DM1/Kadcyla; 100%), pertuzumab (Perjeta; 66%), and other HER2-targeted regimens (54%).⁴ Additionally, ORRs were consistent across subgroups, including those who received at least 3 previous regimens (59%) and those who were previously treated with pertuzumab (64%). The disease control rate was 97%, with only 5 of 184 patients not showing stable disease or better on their first postbaseline scan.⁴ "There were very few patients who progressed. Most patients had a response, but 61% had an actual objective response, and if you think about the median number of prior therapies, that was very impressive,” Isaacs said.

The most common adverse effects (AEs), which were observed in 20% or more of patients, included nausea, fatigue, vomiting,
alopecia, constipation, decreased appetite, anemia, and neutropenia. The adverse effect that we need to think about most, and that was the most concerning, is interstitial lung disease [ILD]. Any grade was about 13.5%, but there were just over 2.0% of patients who had fatal ILD with this drug, which is obviously a very concerning adverse effect,” Isaacs said. Because of this finding, the prescribing information includes a boxed warning advising health care providers of the risk of ILD and pneumonitis, noting that patients need to be carefully monitored for any signs or symptoms of these complications, including cough, dyspnea, fever, and other new or worsening respiratory symptoms.5

“It seemed like, if the drug was continued when you had just abnormalities on x-ray, that could progress very rapidly,” Isaacs said. Although there are no contraindications to using trastuzumab deruxtecan, because of its potential to affect the lungs, Isaacs emphasized that its use needs to be carefully considered in patients with preexisting lung disease, particularly while the world is still grappling with the coronavirus disease 2019 (COVID-19) pandemic. Despite this AE, she noted that it is an exciting drug “whose results showed the most phenomenal waterfall plot that many [clinicians] have seen in a trial.”

**NEWLY APPROVED AND EMERGING TKIs**

Several TKIs, including neratinib (Nerlynx), tucatinib (Tukysa), and pyrotinib, have recently shown benefit in clinical trials when used in combination with capecitabine. Of these, neratinib and tucatinib were recently approved by the FDA based on their clinical trial data.6,7 Both are indicated in adult patients with previously treated advanced or metastatic HER2-positive breast cancer, with neratinib approved for use after failure of at least 2 anti-HER2-based regimens and tucatinib approved for use after failure of at least 1 anti-HER2-based regimen. Notably, the indication for tucatinib includes patients with brain metastases (Table).8,9

**Neratinib**

Neratinib was approved based on the phase 3 NALA trial (NCT01808573), which randomly assigned patients with stage IV HER2-positive breast cancer previously treated with at least 2 prior HER2-directed regimens in the metastatic setting to neratinib plus capecitabine (n = 307) or lapatinib plus capecitabine (n = 314).6,10 The risk of disease progression or death was reduced by 24% in the neratinib arm, with 6- and 12-month progression-free survival (PFS) rates of 47.2% and 28.8% versus 37.8% and 14.8%, respectively. The 6-month overall survival (OS) rate was 90.2% in the neratinib arm versus 87.5% in the lapatinib arm, and the 12-month OS rates were 72.5% versus 66.7% in these arms, respectively.10 “It was noted that a smaller proportion of patients needed intervention for CNS [central nervous system] disease on the neratinib arm compared to lapatinib arm, [but the investigators] did not [include] any data in terms of responses in the brain,” Sharma said.

Treatment-emergent AEs were similar between arms; however, grade 3 diarrhea was significantly more common in the neratinib arm than the lapatinib arm (24.4% vs 12.5%), despite antidiarrhea prophylaxis. “This has been one of the limiting factors in terms of utilization of this drug,” Sharma said.

### TABLE. Prescribing Information for Recent Tyrosine Kinase Inhibitor Approvals for HER2-Positive Breast Cancer6,9

<table>
<thead>
<tr>
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<th>Neratinib (Nerlynx)</th>
<th>Tucatinib (Tukysa)</th>
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<tr>
<td><strong>Indications</strong></td>
<td>In combination with capecitabine for adult patients with HER2-positive breast cancer who have received ≥ 2 previous anti-HER2-based regimens in the metastatic setting</td>
<td>In combination with trastuzumab and capecitabine for adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received ≥ 1 prior anti-HER2-based regimens in the metastatic setting</td>
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<tr>
<td><strong>Dosage/administration</strong></td>
<td>240 mg given orally once daily with food on days 1-21 of a 21-day cycle Must be used with antidiarrheal prophylaxis of concomitant lopera-mide upon first dose of neratinib and continued during the first 56 days of treatment, with lopera-mide dosage then adjusted to maintain 1 to 2 bowel movements daily</td>
<td>300 mg orally twice daily with or without food</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Warnings and precautions</strong></td>
<td>Diarrhea, hepatotoxicity, embryo-fetal toxicity</td>
<td>Diarrhea, hepatotoxicity, embryo-fetal toxicity</td>
</tr>
<tr>
<td><strong>Most common adverse effects</strong></td>
<td>Reported in ≥ 5% of patients treated with capecitabine combination: diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, decreased weight, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasm</td>
<td>Reported in ≥ 20% of patients; diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash</td>
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<td><strong>Drug interactions</strong></td>
<td>Avoid concomitant use with proton pump inhibitors, strong CYP3A4 inhibitors, moderate CYP3A4 and P-glycoprotein (P-gp) dual inhibitors, and strong CYP3A4 inducers Monitor closely for adverse effects when used with P-gp substrates</td>
<td>Avoid concomitant use with strong CYP3A inducers, moderate CYP2C8 inhibitors, and strong CYP3A substrates Consider dose reduction when using with P-gp substrates</td>
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**Tucatinib**

Tucatinib was approved based on data from the phase 2 HER2CLIMB trial (NCT02614794), which randomly assigned 612 patients with locally advanced or metastatic HER2-positive breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1 2:1 to tucatinib, capecitabine, and trastuzumab (n = 410) or to placebo, capecitabine, and trastuzumab (n = 202). The median PFS was 7.8 months in the tucatinib arm and 5.6 months in the placebo arm (HR, 0.54; 95% CI, 0.42-0.71; P < .00001). The confirmed overall response rate for patients with measurable disease was 40.6% and 22.8% in the tucatinib and placebo arms, respectively (P = .00008). Most importantly, tucatinib showed a survival benefit. “There was about a 4.5-month prolongation in OS for the group of women who got the tucatinib on top of the capecitabine and trastuzumab,” Isaacs said. Further, a median OS of 21.9 months in the tucatinib arm compared with 17.4 months in the placebo arm was observed.7

Isaacs emphasized that HER2CLIMB included a large proportion of patients with brain metastases, with just under half having CNS involvement (n = 291), and that these patients also derived benefit from the addition of tucatinib. The median PFS was 7.6 months for tucatinib-treated patients compared with 5.4 months in patients treated with placebo (HR, 0.48; 95% CI, 0.34-0.69; P < .00001).9 “The fact that that benefit is there and it’s an overall survival benefit not limited to patients with brain metastases, but really, at least in the third line, anybody with that higher-exposure HER2-positive disease, I lean toward using tucatinib,” said Tiffany A. Traina, MD. As for the future of the agent, Traina added that it would be wonderful to see a time when tucatinib may find utility in the ability to minimize the development of brain metastases.

Panelist John Fox, MD, MHA, concurred, adding that the HER2CLIMB data were reminiscent of the efficacy of osimertinib (Tagrisso) in patients with EGFR-mutant non-small cell lung cancer. “Osimertinib not only treated brain metastases but also reduced the likelihood of development of them and was subsequently approved as a first-line therapy,” Fox said. “We’ll see if tucatinib makes that same progression from third-line to earlier line therapies.”

**Pyrotinib**

Pyrotinib has been examined in a phase 3 study (NCT02973737) in China, which randomly assigned patients with HER2-positive metastatic breast cancer previously treated with taxanes and trastuzumab 2:1 to pyrotinib plus capecitabine (n = 185) or placebo plus capecitabine (n = 94).10 The median PFS was 11.1 months in the pyrotinib arm and 4.1 months in the placebo plus capecitabine arm. “The pyrotinib trial has this huge PFS benefit, more than what we’ve seen with other oral tyrosine kinase inhibitors, and also a benefit in patients with brain metastases,” moderator Hope S. Rugo, MD, FASCO, said. “The key with that trial is that some of the patients hadn’t received trastuzumab so they were a relatively treatment-naïve group of patients who didn’t have access to other therapies.” When the trial was conducted, said Sharma, pertuzumab was not approved in China and the approval of T-DM1 was recent.

Pyrotinib also showed benefit in the phase 3 PHOEBE trial (NCT03080805), which was presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.12 The trial randomly assigned 267 patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes and/or anthracyclines 1:1 to receive pyrotinib plus capecitabine (n = 134) or lapatinib plus capecitabine (n = 133). The median PFS was 12.5 months in the pyrotinib arm versus 6.8 months in the lapatinib arm (HR, 0.39; 95% CI, 0.27-0.56; P < .0001). Pyrotinib also showed benefit over lapatinib in ORR (67.2% vs 51.5%), clinical benefit rate (73.1% vs 59.1%), and median duration of response (11.1 vs 7.0 months). The most common grade 3 or higher AEs with pyrotinib included diarrhea (30.6%) and hand-foot syndrome (16.4%).12

**Margetuximab**

Margetuximab is an innovative immune-enhancing monoclonal antibody that has shown good clinical activity in the ongoing phase 3 SOPHIA study (NCT02492711).13 “This [drug] was designed to try to increase the binding for the low-affinity activating Fc gamma receptor, which is CD16A, and decrease affinity for the inhibitory Fc gamma receptor,” said Rugo, who is part of the SOPHIA Study Group. This mechanism of action enhances innate immunity and potentiates adaptive immunity, including enhanced clonality of the T-cell repertoire and induction of HER2-specific T- and B-cell responses.13

The SOPHIA study randomly assigned patients with progression of HER2-positive metastatic breast cancer after at least 2 lines of anti-HER2 therapy, including pertuzumab, and 1 to 3 lines of therapy for HER2-positive metastatic breast cancer 1:1 to margetuximab or trastuzumab, both given with investigator’s choice of chemotherapy (ie, capecitabine, eribulin, gemcitabine, vinorelbine).13 Patients in the margetuximab arm had a longer median PFS than those in the trastuzumab arm (5.8 vs 4.9 months; HR, 0.76; 95% CI, 0.59-0.98; P = .033). Results were more pronounced in patients with CD16A genotypes containing a 158F allele, with this subset of margetuximab-treated patients having a median PFS of 6.9 months. Margetuximab also showed a trend toward OS benefit.

“[These] are very interesting data, but it’s difficult to understand exactly how [margetuximab is] going to play a role in terms of all of these other therapies. It still may play a role in the later-line setting. There is a lot of interest in setting the antibody specifically in patients who have the F allele, which is a large majority of patients, so it’ll be interesting,” Rugo said.

Margetuximab is currently being reviewed by the FDA for the treatment of patients with pretreated metastatic HER2-positive breast cancer in combination with chemotherapy.14 The Prescription Drug User Fee Act decision date is set for December 18, 2020.
THE SYNERGY OF CANCER GROWTH¹

EXPLORING MECHANISMS IN THE TUMOR MICROENVIRONMENT (TME) THAT CONTRIBUTE TO TUMOR GROWTH MAY OPEN NEW CANCER TARGETS²⁻⁵

Transforming Growth Factor-β (TGF-β) engineers the TME to support and sustain tumor survival²⁻⁵,⁶

PD-L1 pathway signaling suppresses T-cell activation⁵,⁷

PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor-β; TME, tumor microenvironment.


EMD Serono, Inc. is the biopharmaceutical company of Merck KGaA, Darmstadt, Germany in the US and Canada.

EMD Serono and GSK are committed to working together to bring innovation to the treatment of cancer through the investigation of the TGF-β/PD-L1 pathways.

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