Rugo Sets the Stage for a Busy Year in Breast Cancer

Hope S. Rugo, MD, FASCO

PEER EXCHANGE
Options Expand in Nonmetastatic NSCLC

OncPathways
RET Joins Precision Oncology Ranks

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2020 SABCS

CLINICAL PERSPECTIVES
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TUMOR TYPE UPDATES
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Alexandre A. Jácome, MD, PhD; and Cathy Eng, MD, on COLON CANCER

28-Gene Score May Predict Distant Metastatic Recurrence in Advanced Head and Neck Cancers

BY ALLEN MO, MD, PhD
ARE YOU THINKING DEEP ENOUGH IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too

With each relapse, multiple myeloma becomes increasingly difficult to control. As the disease progresses, very few patients (less than 5%) experience a deep response. However, evidence suggests a deep response may be associated with improved PFS and OS. Therefore, shouldn’t a goal of treatment be to achieve a deep response in as many patients as possible?

The hope is that more patients may achieve a deep response with emerging therapies on the horizon.

Learn more about why depth of response matters in relapsed or refractory multiple myeloma.

Visit ThinkDeepMM.com

OS=overall survival, PFS=progression-free survival.

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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 62.
GAVRETO™—the only once-daily targeted RET therapy for patients with RET+ metastatic NSCLC and advanced thyroid cancers.1

INDICATIONS
GAVRETO (pralsetinib) is indicated for the treatment of:

• Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test
• Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
• Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

IMPORTANT SAFETY INFORMATION
Interstitial Lung Disease (ILD)/Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased aspartate aminotransferase (AST) occurred in 69% of patients, including Grade 3/4 in 5% and increased alanine aminotransferase (ALT) occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 17 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Tumor Lysis Syndrome (TLS): Cases of TLS have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. Common Grade 3/4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased AST, increased ALT, decreased platelets and increased alkaline phosphatase.

Avoid coadministration of GAVRETO with strong CYP3A inhibitors or combined P-gp and strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration cannot be avoided, increase the GAVRETO dose.

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

Please see Brief Summary of full Prescribing Information for GAVRETO on adjacent pages.

INDICATIONS AND USAGE
Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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

RET-Mutant Medullary Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy.

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

RET Fusion-Positive Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with RET fusion-positive advanced or metastatic thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

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

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension
Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years).

Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Hemorrhagic Events
Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Tumor Lysis Syndrome
Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration.

Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing.

Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily.

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

ADVERSE REACTIONS
The following clinically significant adverse reactions are described above:

- Interstitial Lung Disease/Pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic Events
- Tumor Lysis Syndrome
- Risk of Impaired Wound Healing

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

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET-altered solid tumors, including with RET fusion-positive NSCLC (n=220), and RET-altered thyroid cancer (n=138), in ARROW. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

The most common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain...
and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets, and increased alkaline phosphatase.

**RET Fusion-Positive Non-Small Cell Lung Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year.

The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients; fatal adverse reaction which occurred in > 1 patient included pneumonia (n = 3) and sepsis (n = 2).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included pneumonia (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

**Adverse Reactions (≥ 15%) in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
<th>( \text{Grade 1-4 (%)} )</th>
<th>( \text{Grade 3-4 (%)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>74</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>49</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>39</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>35</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>29</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>61</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>58</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>56</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>27</td>
<td>3.2</td>
<td></td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 216 to 218 patients.

Clinically relevant laboratory abnormalities <20% of patients who received GAVRETO included increased phosphate (10%).

**RET-altered Thyroid Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reactions occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included fatigue, pneumonia, and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting,
pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue, and thrombocytopenia.

Adverse Reactions (≥ 15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain1</td>
<td>42</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
</tr>
<tr>
<td>Diarrhea2</td>
<td>34</td>
</tr>
<tr>
<td>Abdominal Pain3</td>
<td>17</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>17</td>
</tr>
<tr>
<td>Stomatitis4</td>
<td>17</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue6</td>
<td>38</td>
</tr>
<tr>
<td>Edema8</td>
<td>29</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
</tr>
<tr>
<td>Headache2</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral Neuropathy9</td>
<td>20</td>
</tr>
<tr>
<td>Dizziness9</td>
<td>19</td>
</tr>
<tr>
<td>Dysgeusia10</td>
<td>17</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Cough11</td>
<td>27</td>
</tr>
<tr>
<td>Dyspnea12</td>
<td>22</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Rash13</td>
<td>24</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
2 Diarrhea includes colitis, diarrhea
3 Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
4 Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
5 Fatigue includes asthenia, fatigue
6 Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
7 Headache includes headache, migraine
8 Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
9 Dizziness includes dizziness, dizziness postural, vertigo
10 Dysgeusia includes ageusia, dysgeusia
11 Cough includes cough, productive cough, upper-airway cough syndrome
12 Dyspnea includes dyspnea, dyspnea exertional
13 Rash includes dermatitis, dermatitis acneiform, eczema, palmoplantar, erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular

* Only includes a Grade 3 adverse reaction

Clinically relevant adverse reactions in <15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>70</td>
</tr>
<tr>
<td>Increased AST</td>
<td>69</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>43</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>41</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>41</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>28</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>28</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>24</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>22</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>67</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>63</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>59</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>31</td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 135 to 138 patients.

Clinically relevant laboratory abnormalities in patients who received GAVRETO included increased phosphate (40%).

**DRUG INTERACTIONS**

Effects of Other Drugs on GAVRETO

**Strong CYP3A Inhibitors**

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose.

**Strong CYP3A Inducers**

Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration of GAVRETO with strong CYP3A inducers cannot be avoided, increase the GAVRETO dose.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant women of the potential risk to a fetus.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or tests, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

Lactation
Risk Summary
There are no data on the presence of pralsetinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Females and Males of Reproductive Potential
Based on animal data, GAVRETO can cause embryolethality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily.

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

Contraception
GAVRETO can cause fetal harm when administered to a pregnant woman.

Females
Advertise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal contraceptives ineffective.

Males
Advertise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

Infertility
Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility.

Pediatric Use
The safety and effectiveness of GAVRETO have been established in pediatric patients with RET fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET-mutant MTC or RET-fusion thyroid cancer.

Animal Toxicity Data
In a 4-week repeat-dose toxicity study in non-human primates, physeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physeal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicity study, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

Geriatric Use
Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

Hepatic Impairment
GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST).

Manufactured for: Blueprint Medicines Corporation, Cambridge, MA 02139, USA
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For more information, go to www.GAVRETO.com or call 1-888-258-7768.
Hope S. Rugo, MD, FASCO, a 2020 Giants of Cancer Care® award winner in the education category, shares her insights into significant developments in the breast cancer field, including findings recently presented at the San Antonio Breast Cancer Symposium. Rugo, whose research into novel therapies and supportive care has helped shape the breast cancer treatment paradigm, is serving as cochair of the 38th Annual Miami Breast Cancer Conference®, which will be held virtually on March 4 to 7, 2021.
IN MARCH 2020, the United States was in the early stages of the coronavirus disease 2019 (COVID-19) pandemic. We shut down the entire country and ground the economy to a halt to slow the spread of the virus. Think about how much uncertainty we were living under.

Nine months later, the FDA approved 2 COVID-19 vaccines under emergency authorization. Before New Year’s Day, millions of Americans had received the vaccine, including frontline physicians and health care providers and nursing home patients, our most vulnerable citizens.

Nine months. Take a moment to let that sink in.

The mainstream media has crafted a narrative about the COVID-19 pandemic that’s almost entirely negative. They have described the US response to the pandemic as blundering from 1 mistake to the next. This narrative is false. There is another way—a more accurate and underappreciated way—to tell the story of the past 9 months. It is a story of heroism, innovation, and precise science, performed under unbelievable pressure.

Let’s not mince words: The United States and the world must appreciate the role of the pharmaceutical industry—the investigators, physicians, and business leaders—who are rescuing the world from COVID-19. It’s the medical breakthrough of our lifetime.

Instead of dwelling on why many in the media are ignoring this, let’s review some facts.

Since the discovery of COVID-19, here is what scientists have accomplished: They identified a novel virus; unlocked and sequenced its genetic code; created new therapies to save lives; and developed multiple safe and effective vaccines using messenger RNA technology, a technology hopefully applicable to future vaccine development. Margaret Liu, MD, a biomedical scientist and member of the MJH Life Sciences® COVID Coalition, called it a breakthrough for mRNA vaccines.

The United States has 2 vaccines approved for emergency use, 1 from Pfizer/BioNTech and another from Moderna, and the AstraZeneca/Oxford vaccine has been approved for emergency use in the United Kingdom. In addition, there are 64 vaccines undergoing clinical trials at the moment, including 20 in phase 3 trials. In the United States and throughout the world, the pharmaceutical industry has answered the call and invested heavily in this effort.

This was the fastest vaccine development program in history, and it’s not even close. David Pride, MD, PhD, a microbiologist at the University of California, San Diego, estimates that vaccines typically take 10 to 15 years to develop. Until the COVID-19 pandemic, the fastest development timeline was 4 years, for the mumps vaccine.

Many government systems moved quickly to lessen the burden of onerous regulations and provide funding so that vaccines could be developed quickly but with rigorous standards. Perhaps it should be a lesson to all of us that regulation and innovation can be calibrated more effectively during “normal” times as industry races to develop new therapies for other epidemics—cancer, diabetes, heart disease, and more.

The next step of the process—distribution of the vaccine—will be as challenging as the development phase, if not more so. But again, the pharmaceutical industry is rising to the occasion. Factories worldwide are working overtime to produce hundreds of millions of vaccine doses.

Less than a month after the Pfizer vaccine was approved, more than 15.4 million doses of vaccine have been distributed throughout the country, and more than 4.6 million individuals have received their first dose, according to CDC data. Many patients are already receiving their second dose.

Every day, more people will be vaccinated. After health care workers and our most vulnerable citizens, other frontline workers will be next. Teachers will be vaccinated so our children can return to school. And soon, all Americans will be able to receive the vaccine.

Remember, we accomplished this in 9 months, with the help, dedication, and expertise of our pharmaceutical industry heroes. Next time you turn on the TV and see negativity, turn it off and imagine instead where we will be in 9 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\textsuperscript{1,2}

**PROVEN TOLERABILITY**

More than double the median MFS with NUBEQA + ADT\textsuperscript{*} vs 18 months with ADT alone\textsuperscript{1}

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

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%)\textsuperscript{4}

**SAME RATE OF PERMANENT DISCONTINUATION**

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

Dose interruptions and reductions due to adverse reactions occurred in 13% and 6%, respectively, of patients treated with NUBEQA + ADT.

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

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

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

\textit{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); \textit{P}=0.003.1,3\textsuperscript{}}

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1309 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treating 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, \textsuperscript{1,3}tC bone scan by BICR, unacceptable toxicity, or withdrawal.1,2

\textsuperscript{1All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased aspartate aminotransferase (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for some lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

Start new patients with up to 2 months free.*

Visit NUBEQAhcp.com

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 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.

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 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.

*The NUBEQA Free Trial Program provides 2 months’ supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions, please call DUDE Access Services at 1-833-337-DUDE (1-833-337-3833) or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions.

ADT=androgen deprivation therapy; BICR=blinded independent central review; CI=confidence interval; CT=computed tomography; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; MRI=magnetic resonance imaging; NR=not reached.
NUBEQA* (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

**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 fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Permanently 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%).

**6.1 Drug Interactions**

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

**7 DRUG INTERACTIONS**

7.1 Effect of Other Drugs on NUBEQA

**7.2 Effects of NUBEQA on Other Drugs**

Breast Cancer Resistance Protein (BCRP) Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

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

7.3 Effect of Food on the Bioavailability of 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)].

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy. Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as possible. NUBEQA treatment can be continued with the next dose as scheduled.

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

**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 (2.2) 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.

**Table 1: Adverse Reactions in ARAMIS**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥ 3 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
<td>0.7</td>
</tr>
</tbody>
</table>

1 Includes fatigue and anemia

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.
Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, 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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6711000BS

Real-World Data Grow Increasingly Relevant in Oncology Practice

by MAURIE MARKMAN, MD

THE IMPORTANCE OF OBJECTIVELY valid data is well established in clinical medicine. Such data include an accurate recording of a patient’s clinical history; evaluation of signs and symptoms of illness; and measurement of various routine indicators, such as granulocyte and platelet counts, serum glucose, electrolytes, and liver function tests, and more specialized biomarkers, such as blood cultures and serum antibody levels to potential infectious pathogens. They also include imaging studies that hopefully help inform the differential diagnosis of a new medical condition or the status of an existing ailment.

In oncology, one must add to these general data elements those more specific to the cancer itself, including pathology, tumor staging, unique radiographic studies, and biological markers of the presence, extent, and progress of the cancer. Specific information related to the impact of treatment on the individual patient through positive signals such as a decrease in tumor markers and negative indicators such as bone marrow suppression must also be added. This description of the relevance of data in cancer management is understood by all who care for patients with cancer.

However, over time there have been rather dramatic, even revolutionary, changes in the types and complexity of clinically relevant data, the methods of recording what is collected (eg, electronic medical record), and the truly massive volume of information available which can positively or negatively influence the quality of care provided and the ultimate outcomes.

For example, one only needs to briefly consider the large number of new antineoplastic agents the FDA has approved for use in individual malignancies (eg, breast, non–small cell lung, colon, renal cell cancers, etc) compared with a mere 10 years ago to appreciate the growing volume of knowledge that oncologists must master to optimally care for patients in a specific clinical setting. The need for robust, easy-to-use, and up-to-date decision support tools is an increasingly critical requirement within the oncology community.

CLINICAL UTILITY OF DATABASES

However, the goal of this commentary is to highlight another critical aspect of the rapid changes in both the quantity of data available and the innovative technology increasingly employed to collect this information. These developments have the potential to truly revolutionize cancer care through the understanding and meaningful use of what has been labeled real-world data.

Consider this hypothetical but certainly very real-world scenario: A 73-year-old modestly obese woman with a more than 25-year history of well-controlled insulin-dependent diabetes who has suffered a silent myocardial infarction 4 months before a diagnosis of metastatic triple-negative breast cancer seeks your recommendation for therapy. Although the patient has documented disease in the lung and bone, her ECOG performance status is 1, and she has no evident cardiac symptoms.

A novel antineoplastic agent was approved for clinical use 1 year ago in this theoretical setting, with the drug shown to substantially improve both progression-free and overall survival rates compared with those of a standard-of-care control arm. Based on published phase 3 trial results, it is difficult to assess clearly the safety of this drug for this individual patient because, not surprisingly, few research participants in this landmark study were: (a) more than 70 years old; (b) modestly obese; (c) had a prolonged history of insulin-dependent diabetes; or (d) had a recent myocardial insult.

However, what if one could easily search a large population database potentially involving thousands of patients
treated outside of clinical trial settings since the introduction of this agent to find a group of individuals with similar baseline characteristics such as age, weight, and comorbidities such as diabetes and recent myocardial injury? Evidence that the drug had been safely delivered in similar patients whose data were available in this database would be reassuring to the physician, the patient, and her family, indicating that using this agent could be a viable option despite the lack of clinical trial data addressing this critical point. Conversely, evidence that serious adverse events were associated with the drug’s administration (eg, hospitalization for complications of diabetes, new cardiac event) would likely and appropriately be an argument against its use.

It is not difficult to see the potential for this strategy; it could help inform clinical decisions in common settings where the current standard of care or novel single agents or combinations are employed in multiple patient populations that are poorly represented in the clinical trials leading to regulatory approval or in subsequently published studies that extended the use of the specific regimens in question.

Another possible use of such real-world databases would be updating information regarding potential adverse events associated with anti-neoplastic strategies appropriately approved for clinical use based on demonstrated efficacy, but with a limited number of patients treated when initial regulatory permission was granted.

For example, TRK inhibitors have been shown to be highly efficacious in a rare group of adult and pediatric cancers with demonstrated NTRK or ROS1 fusion abnormalities. As a result of the quite modest incidence of these cancers, the full spectrum of possible adverse effects, and their severity, was not fully characterized at the time of the initial drug approval. In a recent report, investigators retrospectively reviewed the clinical course of 96 patients treated with this class of agents, which has helped to more fully characterize the risks associated with this therapy, including specific, unique neurological toxicities (eg, withdrawal pain).

Finally, the potential utility of real-world data relates to the precision medicine arena. As more patients undergo advanced genomic testing in the search for unique cancer-specific molecular abnormalities that may be targeted, it is highly likely that oncologists will attempt to treat individual patients “off-label” with a variety of approaches based on existing and rapidly evolving medical knowledge. Hopefully, they would be in a better position to know whether their own patient might be an appropriate candidate to receive a specific therapeutic regimen if these “N-of-1” experiences involving evidence for or against clinical benefit (eg, tumor shrinkage or declines in cancer biomarkers, improvement in cancer-related symptoms, or extended time to subsequent disease progression) in specific clinical settings, such as those with a molecular abnormality detected in a particular tumor type, were combined and made widely available.

Future efforts that ensure essential patient security and privacy will transform rather stagnant data from electronic medical records into vitally relevant information that will help optimize the quality of care and clinical outcomes for the next patient we see in our office.

REFERENCE

Rituximab Biosimilar Gains Approval for 4 Hematologic Indications

Rituximab-arrx (Riabni), a biosimilar to rituximab (Rituxan), is now approved for the treatment of adult patients with non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA; Wegener granulomatosis), and microscopic polyangiitis (MPA).

The biosimilar has the same amino acid sequence as the reference rituximab monoclonal antibody. Further, it has the same strength, dosage form, and route of administration as the intravenous formulation of its reference product. The approval was based on data from a randomized, comparative clinical study of 256 patients who received a 375-mg/m² intravenous infusion of either rituximab-arrx or rituximab. The pharmacokinetics, pharmacodynamics, safety, and immunogenicity of the CD20-directed cytolytic antibody were very similar to those of rituximab.

At the time of launch, rituximab-arrx will be priced 16.7% below the current average selling price of rituximab, according to Amgen, the biosimilar’s developer.

Selinexor Plus Bortezomib/Dexamethasone Approval Expands Eligible Population

Adult patients with multiple myeloma (MM) who have received at least 1 previous therapy can now receive selinexor (Xpovio) in combination with bortezomib and dexamethasone. The combination was approved by the FDA based on data from the pivotal phase 3 BOSTON trial (NCT03110562), in which the selinexor combination resulted in a statistically significant improvement in progression-free survival compared with bortezomib/dexamethasone alone (13.93 vs 9.46 months, respectively; HR, 0.76; 95% CI, 0.59-0.98; \( p = .0033 \)).

The overall response rate in the total study population was 76.4% with the selinexor triplet (n = 195) compared with 62.3% with the doublet (n = 207; \( p = .0012 \)). The median time to response was 1.1 months with the triplet versus 1.4 months with the doublet, and the median duration of response was 20.3 months and 12.9 months, respectively. Benefit was observed across all analyzed subgroups, including those for age, high-risk cytogenetics, frailty, prior proteasome inhibitor treatment, prior receipt of lenalidomide (Revlimid), and number of previous lines of therapy.

Relugolix Gets Green Light for Advanced Prostate Cancer

The oral gonadotropin-releasing hormone receptor antagonist relugolix (Orgovyx) has received FDA approval for the treatment of patients with advanced prostate cancer. The regulatory decision was based on data from the phase 3 HERO trial (NCT03085095) comparing the oral agent with standard long-acting injectable luteinizing hormone–releasing hormone agonists that are commonly used as androgen-deprivation therapy.

Findings from HERO showed that relugolix demonstrated superiority over leuprolide (Lupron) in sustained testosterone (T) suppression through 48 weeks, fast T recovery following discontinuation, and a 50% reduction in major adverse cardiovascular events in patients with advanced disease. Patients were randomized 2:1 to receive either oral relugolix at a once-daily dose of 120 mg following a 1-time 360-mg loading dose (n = 624) or a 3-month depot injection of leuprolide acetate (n = 310).

Specifically, 96.7% (95% CI, 94.9%-97.9%) of patients who were given relugolix achieved and maintained castration through 48 weeks compared with 88.8% (95% CI, 84.6%-91.8%) of those who received leuprolide. All secondary end points evaluated also demonstrated superiority of relugolix over leuprolide (\( P < .0001 \)).

Confirmatory Trials Fail to Support SCLC Indication for Nivolumab

Bristol Myers Squibb has withdrawn nivolumab (Opdivo) from the US market for the treatment of patients with small cell lung cancer (SCLC) who have experienced disease progression after a platinum-based chemotherapy and at least 1 other line of therapy, according to an announcement from the pharmaceutical company.

Data from the confirmatory trials for the agent’s prior accelerated approval, CheckMate 451 (NCT02538666) and CheckMate 331 (NCT02481830), failed to meet their primary end points of overall survival in different treatment settings. Nivolumab had been the first new therapy to receive FDA approval for the adjuvant treatment of patients with SCLC in this setting after nearly 2 decades.

Following a consultation with the FDA, Bristol Myers Squibb decided to withdraw the SCLC indication from the US market. This action was completed in accordance with the regulatory agency’s standard procedures for evaluating accelerated approvals that have not satisfied their postmarketing requirements and as part of a larger, industrywide assessment.

The accelerated approval was based on data from the phase 1/2 CheckMate 032 trial (NCT01928394) of patients with advanced or metastatic solid tumors. In patients with SCLC (n = 109), the agent elicited an objective response rate of 12% (95% CI, 6.5%-19.5%), comprising a partial response rate of 11% and a complete response rate of 0.9%. The median duration of response was 17.9 months (95% CI, 7.9-42.1), with 62% of patients experiencing a continued response at 12 months and 39% at 18 months.

Margetuximab Combo Enters Metastatic HER2+ Breast Cancer Arena

The FDA has approved margetuximab-cmkb (Margenza) in combination with chemotherapy for the treatment of adult patients with metastatic HER2-positive breast cancer who have previously received 2 or more anti-HER2 regimens, at least 1 of which being for metastatic disease.

The approval was based on data from the phase 3 SOPHIA trial (NCT02492711), in which the margetuximab plus chemotherapy combination demonstrated a statistically significant reduction in the risk of disease progression or death of 24% versus trastuzumab (Herceptin) in combination with chemotherapy (HR, 0.76; 95% CI, 0.59-0.98; \( P = .0033 \)). The median progression-free survival with the margetuximab regimen was 5.8 months versus 4.9 months with the trastuzumab regimen (HR, 0.76; 95% CI, 0.59-0.98; \( P = .0033 \)).

Moreover, the objective response rates were 22% and 16%, respectively. Data from the final overall survival analysis of the trial are expected to be released in the second half of 2021, according to MacroGenics, Inc, the developer of margetuximab.
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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 of clinical benefit in confirmatory trials.

INDICATION

PADCEV is indicated for adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. Closely monitor blood glucose levels in patients with diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased in those with and without pre-existing 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 pre-existing 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 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 (SDRIFE), 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.

**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.**

**References:**

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PADCEV® (enfortumab vedotin-ejv) 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 response rate. 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>Severity*</th>
<th>Dose Modification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose &gt;250 mg/dL</td>
<td>Withhold until elevated blood glucose has improved to &lt;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 &lt;1 then, resume treatment reduced by one dose level.</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>
</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>
</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>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue.</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 previous 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 complete resolution, and 28% 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 opthalmic 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 39% had pruritus. Grade 3-4 skin reactions occurred in 10% of patients and included symmetrical drug-related interstitial and flexural exanthema (SDRIFI), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. In study EV-201, the median time to onset of severe skin reactions was 0.8 months (range: 0.2 to 9.8). 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 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 (NCT02081999), 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 of a 28-day cycle until disease progression or unacceptable toxicity. The median duration of exposure to PADCEV was 4.6 months (range: 0.5-15.8).

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 (8%). 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, 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 n=125</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Any</td>
<td>100%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>56%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>56%</td>
</tr>
<tr>
<td>Dyseusia</td>
<td>42%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>52%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>50%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>26%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>26%</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>40%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>45%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
</tr>
</tbody>
</table>

*Includes: asthenia and fatigue
†Includes: hypesthesia, gait disturbance, muscular weakness, neuralgia, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy and peripheral sensorimotor neuropathy.
‡Includes: dermatitis acrocinem, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodynesthesis 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.

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

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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Drug Spotlight  |  PRALSETINIB (GAVRETO)

Pralsetinib Approval Expands Options for RET-Positive Thyroid Cancers

by JASON HARRIS

THE TREATMENT LANDSCAPE in thyroid cancer now includes 2 therapies specifically for patients whose tumors harbor RET alterations. The FDA granted accelerated approval to pralsetinib (Gavreto) on December 1, 2020, for patients 12 years and older with metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy and those with RET fusion–positive thyroid cancer who need systemic therapy and are refractory to prior radioactive iodine therapy, if appropriate.1,2

The decision represents an expanded indication for pralsetinib, which gained its initial FDA approval in September 2020 for adults with metastatic RET fusion–positive non–small cell lung cancer (NSCLC). In May 2020, selpercatinib (Retevmo) became the first RET-specific inhibitor approved for similar RET-altered thyroid and NSCLC indications.3

The latest pralsetinib approval was based on data from the multicenter, open-label phase 1/2 ARROW trial (NCT03037385), in which the agent was evaluated in patients with RET-mutated MTC, thyroid cancer and NSCLC with RET fusions; and other RET-altered solid tumors.

In MTC, pralsetinib induced an overall response rate (ORR) of 60% (95% CI, 46%-73%) among 55 patients with metastatic RET-mutant disease who had received prior cabozantinib (Cometriq/Cabometyx), vandetanib (Caprelsa), or both. The ORR was higher at 66% (95% CI, 46%-82%) among 29 patients with RET-mutant MTC treated with pralsetinib who did not receive previous treatment with cabozantinib or vandetanib.

Among 9 patients with RET fusion–positive thyroid cancer that was also refractory to radioactive iodine, the ORR was 89% (95% CI, 52%-100%) with pralsetinib.

In an interview with OncologyLive®, Lori J. Wirth, MD, a leading investigator into pralsetinib, discussed the potential impact of the drug on the thyroid cancer treatment landscape. Wirth is medical director of the Center for Head and Neck Cancers and the Elizabeth and Michael Ruane Chair of Oncology at Massachusetts General Hospital and an associate professor of medicine at Harvard Medical School, both in Boston, Massachusetts.

What is most significant about the response data in patients with MTC in the ARROW trial?

What’s noteworthy about the data on pralsetinib and patients with RET-mutated MTC is that the drug works really well. The response rate of 60% in patients who had been previously treated with vandetanib and/or cabozantinib is really good in terms of activity. And then the response rates were even higher in patients who had not been previously treated, although that was a smaller group of patients.

The other thing to add about the efficacy of pralsetinib is that not only are we seeing high response rates, but the responses are very durable. So far, the data show that we haven’t yet reached the median duration of response or the median progression-free survival [PFS] in these patients.

How do responses with pralsetinib compare with what you see with standard treatment?

The standard treatments, vandetanib and cabozantinib, are pretty good drugs in MTC in terms of efficacy. Particularly in the vandetanib trial [study D4200C00058; NCT00410761], the response rate exceeded 40%. As of the reporting of that trial, the median PFS had not yet been met, meaning that those patients were having durable responses. We can also see very durable responses with vandetanib and cabozantinib in MTC.

However, the response rates that we’re seeing with RET-specific drugs are higher, and the RET-specific drugs are very well tolerated overall. I don’t know if we’re going to end up seeing, once the data are mature, that the efficacy lasts longer with these RET-specific inhibitors than with the nonspecific multi kinase inhibitors. That remains to be seen. But among the differences in terms of the treatment and the durability, and the idea that patients are on these therapies for many months, is that the toll that the adverse effect profile takes on the patient overall seems to be less with the RET-specific inhibitors.

What mechanisms does pralsetinib employ to block oncogenic RET activity?

Pralsetinib was designed to inhibit the wild-type RET kinase that’s present in those fusion molecules, as well as all of the known mutant RET kinases that we see across various patients with MTC. The drug was designed to be as specific for the RET kinase as possible and to minimize the inhibition of other similar kinases such as VEGFR2.

What unanswered questions need to be addressed in the further development of pralsetinib?

With MTC, many patients have relatively indolent disease that grows very slowly and they may be asymptomatic. So an important question is: Is it better to hold off and wait to initiate therapy until patients have more advanced disease? Or is treatment earlier in the course of illness better?

Unfortunately, we have to expect that pralsetinib is not going to work forever in most patients with metastatic MTC and that we will likely see patients eventually progress and develop acquired resistance. We still need to understand what the mechanisms of acquired resistance will be so that the next generation of treatments for these RET-driven cancers can be designed and studied.

REFERENCES
PIVOTAL CLINICAL TRIAL

ARROW (NCT03037385) is a phase 1/2 multicohort trial that enrolled patients with RET-altered tumors in which patients received pralsetinib monotherapy. The efficacy population for thyroid cancers comprised 93 patients: 55 with RET-mutant metastatic MTC previously treated with cabozantinib (Cometriq/Cabometyx), vandetanib (Caprelsa), or both; 29 with RET-mutant MTC not treated with those drugs; and 9 with RET-fusion–positive thyroid cancer who progressed on standard therapy. RET mutation status was determined by next-generation sequencing, polymerase chain reaction testing, or fluorescence in situ hybridization.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>RET-mutant MTC cohorts</th>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated MTCa</td>
<td>59 (25-83)</td>
</tr>
<tr>
<td>Treatment-naïve MTCa</td>
<td>61 (19-81)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of CNS/brain metastases in MTC cohortsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated</td>
</tr>
<tr>
<td>No prior systemic treatment</td>
</tr>
</tbody>
</table>

Primary RET mutation types in MTC cohortsb

- M918T: 61%
- Cysteine-rich domain: 29%
- V804M/L: 3%
- Other: 7%

EFICACY RESULTS FOR THYROID CANCER COHORTS IN THE ARROW TRIAL

<table>
<thead>
<tr>
<th>RET-mutant medullary thyroid cancer</th>
<th>Previously treateda</th>
<th>Treatment naïvea</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>60% (46%-73%)</td>
<td>66% (46%-82%)</td>
</tr>
<tr>
<td>CR</td>
<td>1.8%</td>
<td>10%</td>
</tr>
<tr>
<td>PR</td>
<td>58%</td>
<td>55%</td>
</tr>
<tr>
<td>Number of responders</td>
<td>N = 33</td>
<td>N = 19</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>NR (15.1-NE)</td>
<td>NR (NE-NE)</td>
</tr>
<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>79% of responders</td>
<td>84% of responders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RET fusion–positive thyroid cancer</th>
<th>Disease progression on standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>89% (52%-100%)</td>
</tr>
<tr>
<td>CR</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>89%</td>
</tr>
<tr>
<td>Number of responders</td>
<td>N = 8</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>NR (NE-NE)</td>
</tr>
<tr>
<td>Patients with DOR ≥ 6 months</td>
<td>100%</td>
</tr>
</tbody>
</table>

CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; ORR, overall response rate; PR, partial response.

aTreatment refers to cabozantinib, vandetanib, or both. Nine patients received systemic therapy other than cabozantinib or vandetanib.

bIncludes all patients enrolled by July 11, 2019, with a data cutoff of February 13, 2020: previously treated MTC (n = 62), treatment-naïve (n = 22).

cGatekeeper mutations.

CNS, central nervous system; MTC, medullary thyroid cancer

WARNINGS AND PRECAUTIONS

- Interstitial lung disease/pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic events
- Tumor lysis syndrome
- Risk of impaired wound healing
- Embryo-fetal toxicity

COMMONLY REPORTED ADVERSE EFFECTS

- Musculoskeletal pain
- Constipation
- Hypertension
- Fatigue
- Diarrhea
- Edema
- Cough
- Rash

Company: Blueprint Medicines Corporation

FDA approval—December 1, 2020

FDA grants accelerated approval to pralsetinib (Gavreto) for treating adult and pediatric patients 12 years and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy or with advanced or metastatic RET-fusion–positive thyroid cancer who require systemic therapy and are refractory to prior radioactive iodine, if appropriate.

Mechanism of action:

- Pralsetinib is a kinase inhibitor of wild-type RET and oncogenic RET fusions (CCDC6-RET) and mutations (RET V804L, RET V804M, RET M918T) with half maximal inhibitory concentrations less than 0.5 nM.
- In purified enzyme assays, pralsetinib also inhibited DDR1, TRXC, FLT3, JAK1/2, TRKA, VEGFR2, PDGFRβ, and FGFR1.

Dosing:

- 400 mg once daily on an empty stomach
  - Food should not be consumed for at least 2 hours before and at least 1 hour after taking pralsetinib.
  - If a dose is missed, it can be taken as soon as possible on the same day. Regular daily dose can resume the next day.
  - Treatment can continue until disease progression or unacceptable toxicity.

Company: Blueprint Medicines Corporation

REFERENCES


WARNINGS AND PRECAUTIONS

- Interstitial lung disease/pneumonitis
- Hypertension
- Hepatotoxicity
- Hemorrhagic events
- Tumor lysis syndrome
- Risk of impaired wound healing
- Embryo-fetal toxicity
- Embryo-fetal toxicity

WARS AND PRECAUTIONS

- Interstitial lung disease/pneumonitis
- Hypertension
- Hepatotoxicity
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COMMONLY REPORTED ADVERSE EFFECTS

- Musculoskeletal pain
- Constipation
- Hypertension
- Fatigue
- Diarrhea
- Edema
- Cough
- Rash

Company: Blueprint Medicines Corporation
COVID-19 in the Clinic

Cytokine Research May Pave the Way for Treating Severe COVID-19

by JASON HARRIS

BY AND LARGE, the patients treated at Mount Sinai Health System during the early days of the coronavirus disease 2019 (COVID-19) pandemic were not dying of the virus, according to Miriam Merad, MD, PhD. In fact, autopsies showed that patients were dying despite clearing the virus.

Investigators did not see a correlation between death and viral load or disease severity. Rather, data from these patients showed that as patients got sicker, they developed a severe inflammatory response.

“The virus was triggering the disease, but it was not really responsible for the organ damage…that we were seeing,” Merad said. An immunologist and oncologist, Merad has spent her career studying inflammation in patients with cancer and was at the right place at the right time to translate her expertise to examine inflammation in patients with COVID-19. She is the Mount Sinai Endowed Professor in Cancer Immunology and director of the Precision Immunology Institute at Icahn School of Medicine at Mount Sinai in New York, New York. She is also the coleader of the Cancer Immunology Program at The Tisch Cancer Institute and director of the Human Immune Monitoring Center (HIMC) at Icahn School of Medicine.

“What we realized was that in those patients with COVID-19, who were getting worse, they had a very severe inflammatory response,” she said. “I discovered the subset of macrophages that is now helping us understand their contribution to disease better.”


She has spent decades investigating macrophages and dendritic cells, which play a critical role in both T-cell activation and T-cell suppression in the context of cancer. Her laboratory has made key discoveries elucidating the mechanisms that control the development and functional identity of dendritic cells and macrophages during homeostasis and understanding how cancer and inflammatory diseases can affect those regulations.

TRANSLATING CANCER RESEARCH TO CRITICAL PRACTICE

Merad and her team, in collaboration with myeloma experts, developed the Ella platform, a rapid cytokine detection system, to measure inflammatory cytokine response to therapy in patients with myeloma. When the time came for an all-hands-on-deck approach to address the pandemic, Merad halted her cancer research and dedicated this platform, along with her laboratory, the HIMC, and the Cancer Immunology Program, to assist in treating patients with COVID-19.

Her laboratory adapted that assay to create a test that detects the inflammatory response to COVID-19 and produces a result within 3 hours. The hypothesis is that with these data it will be easier to anticipate and block inflammatory surge before the patient sustains organ damage.

“We had all these people trained to study the immune system. I told them that we were going to collect [samples from] all the patients [admitted to] the hospital,” she said. “Because of my understanding of macrophages in the context of different diseases, I was able to potentially understand why these macrophage cells were being so activated. There are some similarities between cancer and [the virus], so there is definitely knowledge that we have acquired by studying patients with cancer that has been very useful.”

Although the exact drivers of pathologic inflammation are unknown, Merad and colleagues are interested in identifying the pathways involved in the immune response in order to optimize intervention to control the virus and prevent progressive...
tissue damage that can lead to deleterious hyperinflammation.2

The rapid multiplex cytokine assay was used in patients with COVID-19 admitted to the Mount Sinai Health System between March 21 and April 28, 2020, and measured serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, and IL-1β.1 The test was authorized under an emergency use approval from the New York State Department of Health. In an initial cohort of 1484 patients followed up to 41 days post admission, high serum IL-6 and TNF-α levels at the time of hospitalization were strong and independent predictors of patient survival (P < .0001 and P = .0140, respectively).1

Further, sequential organ failure assessment severity scale scores were available for a subset of 663 patients. Poor survival was associated with IL-6 (HR, 2.9; P < .0001), IL-8 (HR, 1.6; P = .04) and TNF-α (HR, 1.6; P = .03) in these patients.1

“Some of these cells are really the biggest producers of inflammatory cytokine,” Merad said. Her hypothesis is that controlling inflammation could help patients survive COVID-19. “The cells are also involved in other types of diseases, especially inflammatory disease, where they are also activated. Therefore, they’re going to activate T cells and contribute to inflammation-driven injury.”

WHAT LIES AHEAD FOR TRANSLATIONAL RESEARCH

COVID-19 often induces a “cytokine storm,” a severe immune reaction in which the body releases too many cytokines into the blood too quickly. Patients receiving chimeric antigen receptor (CAR) T-cell treatment for leukemia often experience cytokine storm.1

Siltuximab (Sylvant) has been used to treat cytokine storm in patients who received CAR T-cell therapy for cancer. Investigators theorize that suppressing IL-6 might be a treatment option for severe COVID-19. In July, the FDA approved a randomized, double-blind, placebo-controlled phase 3 clinical trial comparing intravenous (IV) siltuximab, an anti-IL-6 monoclonal antibody, versus corticosteroids for patients hospitalized with COVID-19–associated acute respiratory distress syndrome.2

Investigators are also conducting a clinical trial evaluating sarilumab (Kevzara), a human monoclonal antibody against the IL-6 receptor that is indicated for rheumatoid arthritis, as a potential therapy for COVID-19. The agent is concurrently being investigated in combination with capcetabine for HER2-negative metastatic breast cancer in the phase 1/2 EMPOWER trial (NCT0433706).

Results for sarilumab in COVID-19 have been mixed. In July, drug manufacturers Regeneron Pharmaceuticals and Sanofi stopped a phase 3 US trial evaluating the drug in patients requiring mechanical ventilation after the drug failed to meet primary and secondary end points.3 However, Italian investigators in October concluded that IV sarilumab is an option worth pursuing. In an article published in EClinical Medicine, investigators concluded that sarilumab appeared to be a promising short-term approach for patients with COVID-19–related severe pneumonia.4

Mered said that although investigators are close to understanding which inflammatory pathways they need to block, the problem now is that trials are moving forward with small patient populations.

APPLIED RESEARCH. Predicting COVID-19 Severity and Survival1

Objective
Understand the role of inflammatory cytokines on COVID-19 disease course.

Method
An adapted rapid multiplex cytokine test was used to measure IL-6, TNF-α, and IL-1β, as known markers of inflammation and organ damage in 1484 patients with COVID-19 admitted to the Mount Sinai Health System between March 21 and April 28, 2020.

Key takeaways
• Predictors of poor outcome:
  - IL-6
  - TNF-β
  - COVID-19–related cytokine response differed from cytokine storm observed with sepsis and CAR T-cell therapy

Clinical implications
The predictive value of cytokines may guide treatment decisions by stratifying patients who may develop respiratory failure, end organ damage, and death.

SCIENCE AND COMMUNITY STEP UP

In a larger sense, New York City pulled together. Merad said local restaurants provided “fantastic food” to her team on a regular basis. High school students sent cards thanking them for their efforts and local schools sent N95 masks. Even her children got involved, baking cakes for investigators.

Some of her team members refused to leave the hospital and Merad had to force them to go home to rest. Others broke down crying from exhaustion. The experience was so intense and the sense of camaraderie so strong that some of her volunteers cried when she released them back to their normal jobs.

At the first surge of the pandemic in late February and early March, Merad had an “army” of 60 to 80 investigators collecting DNA samples from patients. She and her team worked 12-hour days for weeks on end.

“There was a sense of...facing a war and that we were here together and were fighting together. There was a sense of fighting a war with all members of this community,” she said. “I’ve been here 15 years—I’ve met so many new people, colleagues that I never had the time to meet before.”

Mount Sinai, with locations in Manhattan and Brooklyn, was at the epicenter of the pandemic in the spring. Every resource was devoted to battling the pandemic.

“All the scientists were here to help the clinicians come up with clinical strategies because they were overwhelmed. They didn’t know how to treat patients initially—you can’t treat what you don’t understand. So, it was difficult, and the scientists decided that we were going to go full force.”

“Science stepped up to the front line,” she said. “It was an extraordinary time. There was a lot of bleakness and anxiety and sadness and fear. But there was also an extraordinary sense of collaboration and humanity that came out of the bleakness.”

For a full list of references, see the article at https://bit.ly/2LpskXK.
TAZVERIK is indicated for the treatment of:

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

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

WATCH NOW! 

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

• Secondary Malignancies

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

• Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC0-45h]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who
TAZVERIK® (tazemetostat)

THE OBJECTIVES OF THIS PROGRAM ARE TO:

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

PRESENTERS

John M. Pagel, MD, PhD
Chief of Hematologic Malignancies
Center for Blood Disorders
and Stem Cell Transplantation
Swedish Cancer Institute

John Burke, MD
Associate Chair, US Oncology
Hematology Research Program
Rocky Mountain Cancer Centers

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

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

Drug Interactions
Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.
Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.
Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

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

Please see the Brief Summary of the Prescribing Information on the next pages.
TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION
Consult the package insert for complete prescribing information.

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

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

Dosage Modifications for Contraindications - None.

Warnings and Precautions
Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 688 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.6% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL).

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

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions]; Clinical Trial Experience - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in patients with relapsed or refractory follicular lymphoma enrolled in Cohorts 4 and 5 of Study E7438-G000-101 [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily [n=99]. Among patients receiving TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for greater than one year, and 21% were exposed for 400 mg orally twice daily or longer. Skeletal abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3+ (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
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<tbody>
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<tr>
<td>Decreased platelets</td>
<td></td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td></td>
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<tr>
<td>Increased alanine aminotransferase</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td></td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS
Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A Inhibitors: Co-administration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations [see Clinical Pharmacology], which may increase the frequency or severity of adverse reactions. Avoid co-administration of strong or moderate CYP3A inhibitors with TAZVERIK. If co-administration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose [see Dosage and Administration]. Strong and Moderate CYP3A Inhibitors: Co-administration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations [see Clinical Pharmacology], which may decrease the efficacy of TAZVERIK. Avoid co-administration of moderate and strong CYP3A inducers with TAZVERIK.

Effect of TAZVERIK on Other Drugs - CYP3A Substrates: Co-administration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates [see Use in Specific Populations, Clinical Pharmacology].

USE IN SPECIFIC POPULATIONS
Pregnancy - Risk Summary: Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology], TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [AUC_{ss,inf}] at the 800 mg twice daily dose (see Data). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively. Data - Animal Data: In pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses of ≥80 mg/kg/ approximately 2 times the adult human exposure at the 800 mg twice daily dose. At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

Lactation - Risk Summary: There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for at least 1 week after the final dose.

Females and Males of Reproductive Potential - Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK [see Use in Specific Populations]. Contraception: Females - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective [see Drug Interactions]. Males - Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-1BL, MDS, and AML have been reported clinically and T-1BL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-1BL appears to be greater with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation assay, an in vitro micronucleus assessment in human lymphocytes, an in vivo micronucleus assessment in rats and oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat, however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult male and female reproductive organs [see Use in Specific Populations].

PATIENT COUNSELING INFORMATION - Advise the patient to read the FDA-approved patient labeling (Medication Guide). Secondary Malignancies - Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-1BL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see Warnings and Precautions]. Embryo-Fetal Toxicity - Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations, Nonclinical Toxicology].

Nonclinical Toxicology - Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose [see Use in Special Populations].

Drug Interactions - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit, and grapefruit juice while taking TAZVERIK [see Drug Interactions].

Brief Summary 07/2020
TZ-FL-BR-20-0097
Rx Only
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Hope S. Rugo, MD, FASCO, describes working in medical oncology as a “tapestry” of experiences. In her case, it’s a very rich, complicated piece of art.

The 2020 Giants of Cancer Care® award winner in the education category is at the forefront of the exploration and development of novel targeted therapies and immunotherapy for patients with breast cancer, including combinations that may overcome resistance, and of strategies to alleviate adverse effects of cancer treatment. She serves in leadership roles for several collaborative clinical investigations and is a noted lecturer at conferences throughout the world.

Through it all, Rugo prizes her relationships with patients. She maintains an active clinical practice at the University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, where she is a professor in the Department of Medicine and the director of breast oncology and clinical trials. At UCSF, she leads the Breast Forum, a discussion platform for patients, families, and caregivers.

“It’s that tapestry that really creates this rich experience. I have had amazing interactions with patients who were remarkable and courageous—individuals who I feel really taught me a lot about life and gave me lessons that I brought back to other patients,” Rugo said in a recent interview with OncLive News Network®. “I continuously learn from my patients and I love those interactions. Breast oncology, in some ways, is amazing because we can know an individual for many, many years and see them quite frequently; we know a lot about those patients and their families and how they’re dealing with these incredible challenges.”

GETTING READY FOR MIAMI
Rugo will join other leading breast cancer experts in translating her vast clinical knowledge for oncology specialists at the virtual 38th Annual Miami Breast Cancer Conference® (MBCC), which Physicians’ Education Resource®, LLC (PER®) is hosting March 4 to 7, 2021. PER® named Rugo as its 2020 Educator of the Year in recognition of the role she plays in sharing her insights with the cancer care community.

Patrick I. Borgen, MD, chair of the Department of Surgery and head of Maimonides Breast Center at Maimonides Medical Center in Brooklyn, New York, serves as program chair for MBCC. Rugo is cochairing the conference with Anees B. Chagpar, MD, MBA, MSc, MPH, a professor in the Department of Surgery at Yale School of Medicine in New Haven, Connecticut, and Debu Tripathy, MD, professor and chairman of the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston.

The MBCC agenda always features important new data and expert insights on treatment approaches across the care spectrum and is updated after the San Antonio Breast Cancer Symposium (SABCS 2020) to present the latest information to attendees.

“There are just so many things going on that are really exciting right now in breast cancer,” Rugo said. “Miami Breast is great because it includes the new data in surgery, in radiation oncology, and in medical oncology, and both early-stage and metastatic disease.”

One of the hallmarks of the conference is the give-and-take between speakers and
audience members, which helps to provide valuable perspective on the latest data. MBCC focuses not only on the latest data, but also on how to apply that data in the clinic.

“We do have selected debates about controversial areas,” Rugo said. “We’re going to talk about where we want to de-escalate treatment, where we want to escalate it, and how we’re using our increasing knowledge of cancer biology to apply this information. “We talk a lot about how [treatment] impacts the patient. What are the impacts...in terms of fertility? We’ve talked about cardiac effects, and patient-reported outcomes, how we treat patients who are older versus younger,” she continued. “We really try to cover all of the very clinically pertinent information and the information that’s come out of the most recent presentations and publications. And then there’s the ability to discuss this and ask questions with the presenters, which is, I think, really great.”

Rugo will be putting into perspective the evolving treatment landscape for patients with estrogen receptor-positive, high-risk, early-stage breast cancer and will present data on novel oral therapies. She expects that recent findings involving antibody-drug conjugates (ADCs), tyrosine kinase inhibitors (TKIs), CDK4/6 inhibitors, and the use of circulating tumor DNA as a predictive biomarker will be key points of discussion.

“There have been so many exciting studies presented this year which are practice changing that I think the Miami Breast meeting is a perfect time to really put this all together in a clinically applicable state,” she said. “And by being virtual, you’ll have access to everyone, and in some ways it’s even easier to attend.”

**LOOKING FORWARD TO 2021**

Rugo is anticipating a busy year in breast cancer research, with investigators building upon many recent advancements. She said that noteworthy findings likely to change practice this year and beyond include research presented at SABCS 2020 into the clinical utility of the Oncotype DX Breast Recurrence Score test, immunotherapy in neoadjuvant and metastatic settings, and emerging novel therapies.

Her own research led to a significant development when the FDA approved margetuximab-cmkb (Margenza) in combination with chemotherapy for adults with metastatic HER2-positive breast cancer who have previously received 2 or more anti-HER2 regimens, at least one of which for metastatic disease, in December 2020.

Rugo was the principal investigator for the phase 3 SOPHIA trial (NCT02492711), which showed that the Fc-engineered monoclonal antibody plus chemotherapy reduced the risk for disease progression or death by 24% compared with trastuzumab (Herceptin) plus chemotherapy. The median progression-free survival (PFS) was 5.8 months (95% CI, 5.5-7.0) in the margetuximab-cmkb arm compared with 4.9 months (95% CI, 4.2-5.6) with the trastuzumab regimen (HR, 76; 95% CI, 0.59-0.98; P = .033).1,2

Investigators observed an objective response rate (ORR) of 22% in the margetuximab arm versus 16% with trastuzumab. Drug maker MacroGenics plans to release overall survival (OS) data in the second half of 2021.

The company said that margetuximab is the first HER2-targeted therapy to demonstrate improved PFS compared with trastuzumab in a head-to-head phase 3 clinical trial.

**ADCs and TKIs**

In the past 13 months, the FDA has granted accelerated approvals for 2 novel ADCs: fam-trastuzumab deruxtecan-nxki (Enhertu), for patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting; and sacituzumab govitac-hzvy (Trodelvy), for patients with metastatic triple-negative breast cancer (TNBC) who have received at least 2 prior therapies for metastatic disease.4

In December 2019, the FDA approved trastuzumab deruxtecan based on findings from the DESTINY-Breast01 trial (NCT03248492), in which the agent demonstrated an ORR of 60.3% (95% CI, 52.9%-67.4%), with a 4.3% complete response (CR) rate and a 56% partial response rate among 184 patients. The median duration of response (DOR) was 14.8 months (95% CI, 13.8-16.9).3

In updated results presented at SABCS 2020, the median DOR expanded to 20.8 months. The estimated 12- and 18-month overall survival (OS) rates were 85% (95% CI, 79%-90%) and 74% (95% CI, 67%-80%), respectively. The median PFS was 19.4 months (95% CI, 14.1-not estimable [NE]), and the preliminary median OS, although still immature, was 24.6 months (95% CI, 23.1-NE).5

In April 2020, the FDA approved sacituzumab govitac based on findings from the phase 1/2 IMMU-132-01 trial (NCT01631552), which showed an ORR of 33.3% (95% CI,
Breast Cancer

24.6%–43.1%) with a median DOR of 7.7 months (95% CI, 4.9–10.8). Survival data from the phase 3 ASCENT trial (NCT02574455), presented at the European Society for Medical Oncology Virtual Congress 2020, showed that sacituzumab govitcan improved median OS by more than 5 months compared with chemotherapy (12.1 vs 6.7 months; HR, 0.48; 95% CI, 0.38–0.59; \( P < .0001 \)). Median PFS for participants who received sacituzumab govitcan was 5.6 months (95% CI, 4.3–6.3) compared with 1.7 months (95% CI, 1.5–2.6) for patients who had chemotherapy (HR, 0.41; 95% CI, 0.32–0.52; \( P < .0001 \)).

The ADC also demonstrated an ORR of 35% versus 5% with physician’s choice of chemotherapy. Ten (4%) patients in the experimental arm had CRs compared with 2 (1%) in the control group.

Further, the FDA also approved tucatinib (Tukysa), a HER2-directed TKI, in combination with trastuzumab and capecitabine in April 2020, for patients with advanced unresectable or metastatic HER2-positive breast cancer. The approval includes patients with brain metastases who have received chemotherapy (HR, 0.41; 95% CI, 0.32–0.52; \( P < .0001 \)).

The agency based its decision on results from the HER2CLIMB trial (NCT02614794), in which the tucatinib-containing combination demonstrated a median PFS of 7.8 months (95% CI, 7.5–9.6) compared with 5.6 months (95% CI, 4.2–7.1) for patients who received placebo plus standard therapy (HR, 0.54; 95% CI, 0.42–0.71; \( P < .00001 \)). The median OS was 21.9 months (95% CI, 18.3–31.0) with the addition of tucatinib versus 17.4 months (95% CI, 13.6–19.9) with standard therapy alone (HR, 0.66; 95% CI, 0.50–0.87; \( P = .00480 \)).

At SABCS 2020, investigators reported that the tucatinib regimen reduced the risk of deterioration of health-related quality of life in patients with brain metastases by 49% versus standard therapy (HR, 0.51; 95% CI, 0.28–0.93). We have ADCs that are changing care for HER2-positive and for triple-negative disease with trastuzumab deruxtecan and sacituzumab govitcan. We have now a very potent and less toxic oral TKI, tucatinib, which has been combined with capecitabine and trastuzumab and results in not only improved PFS but improved OS in the metastatic setting and in patients with active brain metastases—very exciting data that have led to new studies,” Rugo said.

“We’re going to see data in the next year about the efficacy of these ADCs in other populations, such as patients with newly defined HER2-low disease—not HER2 positive but not zero by IHC [immunohistochemistry]—and also the ADC sacituzumab govitcan-hzly in [hormone receptor]-positive disease. There are, I think, really intriguing studies that will potentially allow us to further expand the use of this highly effective therapy,” she said.

The adverse event profile of a new therapy also must be taken into consideration, Rugo noted. “It is always important to understand toxicity with novel agents,” she said. “Trastuzumab deruxtecan has a relatively novel toxicity that is worth mentioning as it is so important for clinicians to recognize and understand. Interstitial lung disease [ILD] or pneumonitis can be seen with this ADC, and the mortality in the phase 2 trial was 2.7%. Current guidelines provide careful and detailed recommendations for managing this toxicity—holding the ADC for grade 1 asymptomatic ILD seen only on imaging, and permanently discontinuing along with steroid treatment for grade 2.”

**CDK4/6 Inhibitors**

According to Rugo, data presented at SABCS 2020 suggest an exciting future for CDK4/6 inhibitors. Results from an updated analysis of the phase 3 MONALEESA-7 trial (NCT02278120) showed that adding ribociclib (Kisqali) to endocrine therapy continued to significantly improve OS and delay subsequent chemotherapy compared with placebo, irrespective of endocrine partner, in pre- and peri-menopausal patients with hormone receptor-positive, HER2-negative breast cancer in combination with suppression of ovarian function.

At a median follow-up of 53.5 months (range, 46.9–66.4), median OS with ribociclib plus endocrine treatment was 58.7 months versus 48.0 months with placebo/endocrine therapy (HR, 0.763; 95% CI, 0.608–0.956), translating into a 24% relative reduction in risk of death with the CDK4/6 inhibitor.

“We saw the updated survival data for MONALEESA-7, [which were] very impressive in young women,” Rugo said.

The conference also featured the primary outcome findings from monarchE (NCT0315997). The phase 3 trial tested the CDK4/6 inhibitor abemaciclib (Verzenio) in combination with standard-of-care endocrine therapy versus endocrine therapy alone in 5637 patients with HER2-positive, hormone receptor-positive, node-positive, high-risk early breast cancer.

Results showed that adding abemaciclib significantly improved invasive disease-free survival (iDFS) compared with standard endocrine therapy alone (HR, 0.713; 95% CI, 0.583–0.871; \( P = .0009 \)) in the intention-to-treat population. This translated into a 28.7% relative reduction in the risk of developing an iDFS event.

In further analysis of the study data, investigators suggested that high expression of Ki-67, a protein marker of cellular proliferation, potentially could be used in conjunction with clinicopathological features to indicate which patients have a greater risk of recurrence and might have the greatest benefit from the addition of the CDK4/6 inhibitor.

Although patients benefited from abemaciclib therapy regardless of Ki-67 expression, outcomes were worse for those with a high level, defined as 20% or greater on IHC testing. These patients had a lower rate of 2-year iDFS of 91.3% (95% CI, 88.9%–93.2%) compared with 94.7% (95% CI, 92.8%–96.1%) for patients with a Ki-67 low score.

CONTINUED ON PAGE 34

**Hope S. Rugo, MD, FASCO, was honored with a 2020 Giants of Cancer Care® award in the education category and as Physicians’ Education Resource®, LLC (PER®)’s 2020 Educator of the Year.**
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The study marked the first time the prespecified threshold for high Ki-67 was used prospectively with a standardized assay in a phase 3 trial, investigators said. Rugo is excited about the potential for its use as a biomarker. "It's not just clinical features, like stage and grade, but also Ki-67 is emerging as an incredibly important factor," Rugo said. "I think this is likely to be practice changing in the next year.”

**Targeted Therapy**

Findings that Rugo and colleagues presented at SABCS 2020 for alpelisib (Piqray), a PI3K inhibitor, are likely to inform treatment choices for a subset of patients with hormone receptor-positive, HER2-negative progressive metastatic disease. In the ongoing phase 2 BYLieve trial (NCT03056755), investigators are evaluating alpelisib in patients with previously treated PIK3CA-mutant hormone receptor-positive, HER2-negative advanced breast cancer.12

The trial has 3 arms: cohort A, testing alpelisib plus fulvestrant (Faslodex) in patients whose immediate prior treatment was a CDK4/6 inhibitor plus an aromatase inhibitor (AI); cohort B, evaluating alpelisib plus letrozole in patients whose immediate prior treatment was a CDK4/6 inhibitor plus fulvestrant; and cohort C, testing alpelisib plus fulvestrant in patients who progressed on or after AI therapy and then received chemotherapy or endocrine therapy as their immediate prior treatment.12

Results were presented for 115 patients in cohort B, in which 82% of participants had progressed on prior AI therapy. A total of 46.1% of patients were alive without disease progression at 6 months per local investigator assessment (n = 53; 95% CI, 36.8-55.6), meeting the primary end point of the study. At a median follow-up of 15 months, the combination of alpelisib and letrozole led to a median PFS of 5.7 months (95% CI, 4.5-7.2).

"In this cohort, the majority of patients had previously been exposed to an AI and had had progression on that treatment, so this is really the most endocrine-resistant population that has been treated with alpelisib combined with an endocrine therapy," Rugo said. The median PFS, she noted, is "quite impressive" for a patient population treated with an AI after exhibiting resistance to an AI.

**MAKING A MARK IN THE FIELD**

The research Rugo presented at SABCS 2020 provides a glimpse at her expansive accomplishments as a clinical investigator, starting in the late 1980s while she was a hematology and oncology fellow at UCSF.

Over the years, she has served as the principal investigator in more than 60 clinical trials, many of which led to major discoveries. Specifically, Rugo led studies exploring the use of agents such as palbociclib (Ibrance) and abemaciclib, and was a member of the steering committees for multiple clinical trials including for the ABRAZO and EMBRACA studies (NCT02034916 and NCT01945775) evaluating the PARP inhibitor talazoparib (Talzenna) in patients with BRCA-mutant metastatic breast cancer.

In the immunotherapy field, Rugo was a primary investigator for the IMpassion130 trial (NCT02425891), which led to the March 2019 FDA approval of atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane) for patients with unresectable, locally advanced PD-L1-positive TNBC. This marked the first immune checkpoint inhibitor to be approved for the treatment of breast cancer.13

She also was on the steering committee for the KEYNOTE-355 trial (NCT02819518) testing pembrolizumab (Keytruda) plus chemotherapy for patients with TNBC and presented a subset update at SABCS 2020. The results of this trial led to FDA approval of pembrolizumab plus either nab-paclitaxel, paclitaxel, or gemcitabine with carboplatin for PD-L1-positive TNBC in November 2020.14

Rugo is actively involved in the multicenter adaptively randomized I-SPY 2 trial, where she is chair of the safety committee and serves on the novel agent committee, publishing the results of 1 of the first arms of the trial (paclitaxel plus veliparib-carboplatin).15 Rugo also has made relieving toxicities of cancer treatment part of her mission. She was the principal investigator for a study evaluating the DigniCap Scalp Cooling System, which uses scalp cooling technology to help prevent chemotherapy-related hair loss. In 2017, DigniCap became the first FDA-approved cooling cap for patients with solid tumors.16 She also led the 2017 SWISH trial (NCT02069093), which investigated a dexamethasone-based mouthwash that reduces stomatitis and mouth and lip inflammation in patients with metastatic breast cancer receiving treatment with everolimus (Afinitor). Findings showed that the oral solution reduced the severity of stomatitis, and the mouthwash has been used ever since.17

"These are projects we all have worked on together and as a community have been able to really make a difference for patients who are being treated with these agents—understanding the time course of toxicity,” she explained. “These have been really great to work on.”

One of Rugo’s lasting contributions to the field is likely to be in training junior faculty and helping patients and their families understand their options for treatment. She also runs UCSF’s Breast Forum, an open bimonthly evening educational session for patients with breast cancer and their families and friends.

Rugo is a master educator and clinician, according to Laura J. Esserman, MD, MBA, the 2018 Giants of Cancer Care® award winner in the cancer diagnostics category. "Not only is she good at educating residents and other physicians and scientists, but she is fantastic at educating her patients about what their risks are, what their options are,” said Esserman, the Alfred A. de Lorimier Endowed Chair in General Surgery and director of the Carol Franc Buck Breast Care Center at UCSF Helen Diller Family Comprehensive Cancer Center. "She has that amazing talent for putting information together in such a way that people can make better decisions."

According to Rugo, her experiences in medical education not only taught her how to convey information, but also help her better relate to her patients and colleagues. She considers herself "very fortunate" to have worked in the field, both nationally and internationally, and credits her career choice and focus to her mother, who died of breast cancer more than 20 years ago.

"That also gives you lots of ideas about clinical research and it keeps you in touch with the community at large," she said. “Then you learn a lot about other cultures and how people manage different aspects of both cancer care and life and death issues as well—that’s been an amazing experience.”

For a full list of references, see the article at Onelive.com.
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Menopausal Status May Inform Need for Chemotherapy in Select Patients With Breast Cancer

by CAROLINE SEYMOUR

Adding chemotherapy to endocrine therapy led to an improvement in 5-year invasive disease-free survival (iDFS) and overall survival (OS) in premenopausal but not postmenopausal women with hormone receptor–positive, HER2-negative, lymph node–positive breast cancer and a recurrence score between 0 and 25. The findings from a prespecified interim analysis of the phase 3 RxPONDER trial (NCT01272037) were presented during the virtual 2020 San Antonio Breast Cancer Symposium (SABCS).

In premenopausal patients, the 5-year iDFS rate was 94.2% in the chemotherapy/endocrine therapy arm versus 89.0% in the endocrine-alone arm, reflecting an absolute difference of 5.2% (adjusted HR, 0.54; 95% CI, 0.38-0.76; \( P = .0004 \)). In postmenopausal patients, the 5-year iDFS rates were 91.6% and 91.9%, respectively (adjusted HR, 0.97; 95% CI, 0.78-1.22; \( P = .82 \)).

“This [treatment strategy] will save tens of thousands of women the time, expense, and potentially harmful side effects that can be associated with chemotherapy infusions,” Kalinsky added. “[However,] premenopausal women with positive nodes and recurrence scores between 0 and 25 are still likely to benefit significantly from chemotherapy.”

Patients with hormone receptor–positive, HER2-negative, lymph node–positive breast cancer have an increased risk of recurrence and are typically treated with chemotherapy.

To prevent potential overtreatment or undertreatment, investigators used the 21-gene Oncotype Dx Recurrence Score to identify which patients with lymph node–negative, hormone receptor–positive, HER2-negative disease can omit chemotherapy.

In lymph node–negative patients, exploratory findings from the phase 3 TAILORx trial (NCT00310180) suggested that women over the age of 50 years with a recurrence score of 25 or less derive no benefit from chemotherapy, whereas patients aged 50 or under with a recurrence score between 16 and 25 may derive benefit from chemotherapy. However, whether these results were generalizable to the approximately 20% of patients in the United States who have nonmetastatic hormone receptor–positive, HER2-negative disease and 1 to 3 positive lymph nodes had not been previously defined.

To that end, investigators launched RxPONDER, a trial in which 5015 patients with a recurrence score between 0 and 25 were randomized to endocrine therapy alone or chemotherapy followed by endocrine therapy. Patients with a recurrence score of more than 25 were treated off study with chemotherapy followed by endocrine therapy.

Patients in the randomized portion of the trial were stratified by recurrence score (0-13 vs 14-25), menopausal status (pre vs post), and nodal surgery (axillary lymph node dissection vs sentinel lymph node biopsy).
Eligible patients included women 18 years or older with at least 1% estrogen receptor and/or progesterone receptor expression, HER2 negativity, 1 to 3 positive lymph nodes, and recurrence scores of 25 or less without distant metastases. They also had to have an ability to receive taxane and/or anthracycline-based chemotherapy.

iDFS, defined as local, regional, distant recurrence, or any second invasive cancer or death due to any cause, served as the primary end point of the study. OS served as the secondary end point.

Additional results demonstrated that the iDFS benefit also translated into an OS benefit in premenopausal patients (TABLE). In this population, the 5-year OS rate was 98.6% with chemotherapy/endocrine therapy versus 97.3% with endocrine therapy alone, reflecting an absolute improvement of 1.3% (adjusted HR, 0.47; 95% CI, 0.24-0.94; P = .032). However, in postmenopausal women, the 5-year OS rates were 96.2% and 96.1%, respectively (adjusted HR, 0.96; 95% CI, 0.70-1.31; P = .79).

Providing additional perspective during the press briefing, SABCS codirector C. Kent Osborne, MD, founding director of the Dan L Duncan Comprehensive Cancer Center and the Dudley and Tina Sharp Chair for Cancer Research at Baylor College of Medicine in Houston, Texas, added, “The results clearly show no benefit to adding chemotherapy to standard endocrine therapy in postmenopausal patients, despite having positive nodes, emphasizing that node positivity, while an important prognostic marker, is not a predictive marker of chemotherapy sensitivity.”

“In premenopausal patients, a different result was obtained. Is the difference in outcome in this subset due to the endocrine effects of chemotherapy? Unfortunately, we may never know the answer to this question,” Osborne concluded.

**REFERENCE**
Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy +/- chemotherapy in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007 (RxPONDER). Presented at: 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020; virtual. Abstract GS1-00.

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**TABLE. RxPONDER Survival Results Stratified by Menopausal Status**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Postmenopausal</th>
<th></th>
<th>Premenopausal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ET (n = 1675)</td>
<td>CET (n = 1675)</td>
<td>ET (n = 831)</td>
<td>CET (n = 834)</td>
</tr>
<tr>
<td>iDFS</td>
<td>91.9% (HR, 0.97; 95% CI, 0.78-1.22; P = .82)</td>
<td>91.6%</td>
<td>89.0%</td>
<td>94.2% (HR, 0.54; 95% CI, 0.38-0.76; P = .0004)</td>
</tr>
<tr>
<td>5-year iDFS difference</td>
<td>NA</td>
<td>5.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>96.1%</td>
<td>96.2% (HR, 0.96; 95% CI, 0.70-1.31; P = .79)</td>
<td>97.3%</td>
<td>98.6% (HR, 0.47; 95% CI, 0.24-0.94; P = .032)</td>
</tr>
<tr>
<td>5-year OS difference</td>
<td>NA</td>
<td>1.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CET, chemotherapy plus endocrine therapy; ET, endocrine therapy; iDFS, invasive disease-free survival; NA, not available; OS, overall survival.

*No statistically significant iDFS difference.

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**Adjuvant Abemaciclib Sustains iDFS Benefit in High-Risk Hormone Receptor–Positive Early Breast Cancer**

by **GINA MAURO**

**THE COMBINATION OF ABEMACICLIB** (Verzenio) and standard endocrine therapy showed a 28.7% reduction in the risk of invasive disease recurrence or death compared with endocrine therapy alone in patients with high-risk, early hormone receptor–positive, HER2-negative breast cancer. The findings from a primary outcome analysis of the phase 3 monarchE trial (NCT03155997) were presented during the 2020 San Antonio Breast Cancer Symposium.1,2

Specifically, results showed that with 395 events and a median follow-up of 19.0 months, the invasive disease-free survival (iDFS) benefit was statistically significant and clinically meaningful (HR, 0.713; 95% CI, 0.583-0.871; 2-sided P = .0009). The 2-year iDFS rates were 92.3% and 89.3% with abemaciclib and endocrine therapy alone, respectively, translating to a 3.0% difference.1

“Abemaciclib combined with standard endocrine therapy continued to demonstrate a reduction in the risk of developing iDFS and distant relapse-free survival [DRFS] events for patients with hormone receptor–positive, HER2-negative, high-risk early breast cancer, and resulted in a statistically significant improvement in iDFS in patients with high Ki-67 tumors,” said senior study author Priya Rastogi, MD, associate professor of medicine at the University of Pittsburgh School of Medicine, in a press briefing ahead of the virtual meeting. “Abemaciclib in combination with endocrine therapy is the first CDK4/6 inhibitor to demonstrate efficacy and tolerability for [this patient population].”

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**REFERENCE**
Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy +/- chemotherapy in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007 (RxPONDER). Presented at: 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020; virtual. Abstract GS1-00.
Abemaciclib is an oral, continuously dosed CDK4/6 inhibitor approved by the FDA for the treatment of patients with hormone receptor–positive/HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal agent, fulvestrant, or as monotherapy.\(^1\)

In monarchE, patients with hormone receptor–positive/HER2-negative, node-positive, high-risk early breast cancer were enrolled into 1 of 2 cohorts: one was based on clinicopathological risk factors, which included 4 or more positive axillary lymph nodes (ALNs) or 1 to 3 ALNs and at least a grade 3 histology or a tumor size 5 cm or larger; the second cohort was based on Ki-67 status and comprised patients with 1 to 3 ALNs, a centrally tested Ki-67 index of 20% or higher, no grade 3 histology, and a tumor size below 5 cm. The intention-to-treat (ITT) population (n = 5637) included patients in both cohorts.

All patients were randomized 1:1 to receive standard endocrine therapy for 5 to 10 years as clinically indicated alone or with abemaciclib at 150 mg twice daily for up to 2 years. Patients were stratified based on prior chemotherapy, menopausal status, and region.

The primary end point of the trial was iDFS based on standardized definitions for efficacy end points criteria. Secondary outcome measures included iDFS in the Ki-67-high (≥ 20%) population (n = 2498), DRFS, overall survival (OS), safety, patient-reported outcomes, and pharmacokinetics.

Data from an earlier interim analysis, which were presented during the European Society for Medical Oncology Virtual Congress 2020, showed that at a median follow-up of 15.5 months, 323 invasive disease-free events occurred. Further, abemaciclib reduced the risk of invasive disease by 25.3% versus endocrine therapy alone (HR, 0.747; 95% CI, 0.598-0.932; 2-sided P = .0096).\(^1\) Additionally, the 2-year iDFS rates were 92.2% in the abemaciclib arm versus 88.7% in the endocrine-alone arm, reflecting an absolute improvement of 3.5%.

Ki-67 was evaluated in all patients in cohorts 1 and 2 with suitable untreated breast tissue.

Additional findings at the primary outcome analysis showed that in the Ki-67-high population, the risk of developing an iDFS event was reduced by 30.9% with abemaciclib (HR, 0.691; 95% CI, 0.519-0.920; 2-sided P = .0111), which was statistically significant and clinically meaningful in this subgroup. The 2-year iDFS rates were 91.6% with abemaciclib and 87.1% with endocrine therapy alone, which translated to a 4.5% difference.

When evaluating for DRFS in the ITT population, investigators found that abemaciclib reduced the risk of DRFS by 31.3% versus endocrine therapy (HR, 0.687; 95% CI, 0.551-0.858; 2-sided P = .0009), which was a clinically meaningful benefit. The 2-year DRFS rates were 93.8% and 90.8%, respectively, which was a 3.0% difference favoring abemaciclib.

The safety data of the abemaciclib regimen are consistent with the findings reported in the second interim analysis and the known tolerability profile of the CDK4/6 inhibitor. Most discontinuations, due to adverse effects (AEs), occurred within the first 5 months of study treatment. Additionally, most patients who required dose holds or reductions could remain on therapy.

At this analysis, the most common AEs were diarrhea, fatigue, and neutropenia, according to Rastogi. Rare AEs included interstitial lung disease and venous thromboembolism, she added.

C. Kent Osborne, MD, founding director of the Dan L. Duncan Comprehensive Cancer Center and the Dudley and Tina Sharp Chair for Cancer Research at Baylor College of Medicine in Houston, Texas, provided commentary on the phase 3 findings.

“The additional 4 months’ follow-up of this trial...continues to show improved invasive disease-free survival for the addition of abemaciclib to standard endocrine therapy in a very high-risk group of patients with hormone receptor-positive breast cancer. I think these results are very encouraging, especially in the subgroup of tumors with high proliferation,” Osborne said. “Caution in these data is needed, given the still rather short follow-up; that estrogen receptor-positive disease is known for its persistent recurrence rate, even past 10 years; and given that this class of inhibitors is largely cytostatic rather than cytotoxic, meaning that it blocks cell proliferation rather than killing the cells. An important question remains: Will the invasive disease-free survival curves come together when the drug is stopped? With these caveats in mind, this is still a very important trial.”

The monarchE trial is ongoing until the final assessment for OS; all patients will be followed for 10 years, Rastogi concluded.

\(\text{REFERENCES}\)


The ELAINE Study is evaluating an investigational oral drug in postmenopausal women with ER+/HER2-breast cancer whose disease has shown progression on previous AI treatment in combination with a CDK 4/6 inhibitor and with an acquired estrogen receptor 1 (ESR1) mutation.*

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• Have been diagnosed with an acquired ESR1 mutation. This may have been detected in previous testing and if not, a blood test as part of the study will be done to see if the mutation is present
• Had disease progression after taking an AI in combination with a CDK 4/6 inhibitor*

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*Als include Arimidex (anastrozole), Femara (letrozole), or Aromasin (exemestane). CDK 4/6 inhibitors include Kisqali (ribociclib), Ibrance (palbociclib), and Verzenio (abemaciclib).

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ER, estrogen receptor; HER, human epidermal receptor.

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Neratinib Leads to Fewer Deaths, CNS Benefit in Early-Stage HER2+ Breast Cancer

by JESSICA HERGERT

AT 8 YEARS OF FOLLOW-UP, fewer deaths and improved cumulative incidence of central nervous system (CNS) recurrences were reported with adjuvant neratinib (Nerlynx) compared with placebo in patients with early-stage HER2-positive breast cancer after trastuzumab (Herceptin)-based therapy, according to results of the final protocol-defined analysis of the phase 3 ExteNET trial (NCT00878709) presented at the 2020 San Antonio Breast Cancer Symposium.

In the intention-to-treat (ITT) population, 8.9% of patients who received neratinib (n = 1420) died prior to the analysis cutoff date compared with 9.6% of patients who received placebo (n = 1420).

Notably, patients who received neratinib had consistently fewer CNS events compared with placebo. The cumulative incidence of CNS recurrences in the ITT population was 1.3% (95% CI, 0.8%-2.1%) with neratinib versus 1.8% (95% CI, 1.2%-2.7%) with placebo.

At 5 years, the Kaplan-Meier estimated rate of CNS disease-free survival (DFS) in the ITT population was 97.5% (95% CI, 96.4%-98.3%) with neratinib (n = 29 events) versus 96.4% (95% CI, 95.2%-97.4%) with placebo (n = 42 events; HR, 0.73; 95% CI, 0.45-1.17).

Neratinib is the first HER2-directed agent to show a trend toward improved CNS outcomes in early-stage HER2-positive breast cancer with consistently fewer CNS events observed in the neratinib arm in all groups reported,” lead study author Frankie Ann Holmes, MD, a retired breast medical oncologist, said in a poster presentation of the data.

However, no statistically significant improvement in overall survival (OS) was observed between arms (TABLE). The estimated 8-year OS rate was 90.1% in the neratinib group versus 90.2% in the placebo group (stratified HR, 0.95; 95% CI, 0.75-1.21; P = .6916).

The multicenter, double-blind, placebo-controlled ExteNET trial randomized patients to receive 240 mg of daily neratinib or placebo for 1 year. The trial enrolled patients with stage I to IIC HER2-positive primary breast cancer who received locoregional treatment and completed trastuzumab-based adjuvant therapy, with or without neoadjuvant therapy, within 2 years of randomization.

In February 2010, per amendment to the protocol, recruitment was restricted to higher-risk patients with stage II to IIC disease who completed trastuzumab-based therapy within 1 year of randomization; patients who completed neoadjuvant therapy and did not achieve a pathological complete response (pCR) also qualified.

Within the ITT population, 57% (n = 816) of patients who received neratinib were hormone receptor-positive, 76% (n = 1085) were node positive, and 62% (n = 884) received concurrent trastuzumab and chemotherapy.

Additionally, among hormone receptor-positive patients who received prior trastuzumab within 1 year of randomization (n = 1334), 81% were node positive, and 61% received concurrent trastuzumab and chemotherapy. Furthermore, 89% of hormone receptor-positive patients who did not achieve a pCR (n = 131) were node positive, and 69% of these patients had concurrent trastuzumab and chemotherapy.

Across hormone receptor-positive subgroups, baseline patient characteristics were similar to the ITT population and those who received placebo.

Prior findings from the ExteNET study demonstrated a 2.5% absolute benefit in 5-year invasive disease-free survival with neratinib (iDFS; HR, 0.73; 95% CI, 0.57-0.92) and a 1.7% absolute benefit in 5-year distant disease-free survival (DDFS; HR, 0.78; 95% CI, 0.60-1.01) in the ITT population.

Moreover, patients with hormone receptor-positive disease who received trastuzumab-based therapy within 1 year of randomization had a 5.1% absolute benefit in 5-year iDFS (HR, 0.58; 95% CI, 0.41-0.82) and a 4.7% absolute benefit in 5-year DDFS (HR, 0.57; 95% CI, 0.39-0.83). Patients with hormone receptor-positive disease who did not achieve a pCR from trastuzumab-based therapy achieved 7.4% (HR, 0.60; 95% CI,

### TABLE. Select Efficacy Outcomes in the ExteNET Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT population</th>
<th>Hormone receptor–positive ≤ 1 year*</th>
<th>Hormone receptor–positive ≤ 1 year no pCR*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Neratinib (n = 1420)</td>
<td>Placebo (n = 1420)</td>
<td>Neratinib (n = 670)</td>
</tr>
<tr>
<td>8-year OS rate</td>
<td>90.1% (0.75-1.21)</td>
<td>90.2%</td>
<td>91.5% (95.2%-97.4%)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.45-1.17)</td>
<td>0.69 (0.55-1.13)</td>
<td>0.41 (0.18-0.85)</td>
</tr>
<tr>
<td>5-year CNS disease-free survival (95% CI)</td>
<td>97.5% (96.4%-98.3%)</td>
<td>96.4% (95.2%-97.4%)</td>
<td>98.4% (95.2%-97.4%)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.45-1.17)</td>
<td>0.69 (0.55-1.13)</td>
<td>0.41 (0.18-0.85)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; ITT, intention to treat.
*Patients who received prior trastuzumab within 1 year of randomization.
High-risk patient group with residual disease after neoadjuvant therapy.
0.33-1.07) and 7.0% (HR, 0.61; 95% CI, 0.32-1.11) absolute benefits, respectively.

Subgroup analyses from the updated 8-year data showed that OS findings were consistent with iDFS findings. OS was numerically improved in hormone receptor-positive patients who received neratinib (91.6%) compared with those who received placebo (90.1%; HR, 0.80; 95% CI, 0.58-1.12). However, neratinib versus placebo did not appear to improve OS among hormone receptor-negative patients (n = 1209), with OS rates of 88.1% and 90.3%, respectively (HR, 1.18; 95% CI, 0.83-1.69).

In the hormone receptor-positive patients who received trastuzumab within 1 year prior to randomization, 7.9% of patients who received neratinib died compared with 10.2% of those who received placebo. The estimated OS rates were 91.5% and 89.4%, respectively (HR, 0.79; 95% CI, 0.55-1.13).

Patients with hormone receptor-positive disease who had residual disease (no pCR) reported an 8-year OS rate of 91.3% with neratinib versus 82.2% with placebo, which translated to an absolute benefit of 9.1% (HR, 0.47; 95% CI, 0.23-0.92). Patients who achieved a pCR reported 8-year OS rates of 93.3% and 73.7%, respectively, reflecting an absolute benefit of 19.6% (HR, 0.40; 95% CI, 0.06-1.88).

“Although the powered OS analysis in the ITT population did not achieve statistical significance, descriptive analyses suggest that there is a trend that neratinib may improve OS in the hormone receptor-positive, ‘less than 1 year [since trastuzumab-based therapy]’ population and in the no pCR group,” Holmes explained.

Regarding CNS recurrence, patients with hormone receptor-positive disease who received trastuzumab within 1 year of randomization as well as patients who received neoadjuvant therapy, irrespective of pCR status, had a lower number of CNS events.

In the hormone receptor-positive population who received trastuzumab-based therapy within 1 year prior to randomization, the estimated CNS-DFS rate was 98.4% (95% CI, 96.8%-99.1%) with neratinib (n = 9 events) and 95.7% (95% CI, 93.6%-97.2%) with placebo (HR, 0.41; 95% CI, 0.18-0.85).

Further stratification showed that the estimated CNS-DFS rate for patients who did not receive prior neoadjuvant therapy (n = 980) was 98.2% (95% CI, 96.3%-99.2%) with neratinib and 97.5% (95% CI, 93.5%-98.6%) with placebo (HR, 0.70; 95% CI, 0.25-1.82). Among patients who did receive prior neoadjuvant therapy (n = 354), the estimated CNS-DFS rates were 98.7% (95% CI, 94.8%-99.7%) and 91.2% (95% CI, 85.1%-94.8%), respectively (HR, 0.18; 95% CI, 0.03-0.63).

Finally, the estimated CNS-DFS rate among patients who did not achieve a pCR was 98.4% (95% CI, 93.6%-99.6%) with neratinib and 92.0% (95% CI, 85.6%-95.7%) with placebo (HR, 0.24; 95% CI, 0.04-0.92).

Among patients who did achieve a pCR, the CNS-DFS rate was 100% (95% CI, 100%-100%) with neratinib and 81.9% (95% CI, 53.1%-93.9%) with placebo (HR, 0; 95% CI, not estimable-1.08).

Additionally, the uptake of anticancer medications, including endocrine therapy, HER2-directed therapy, and chemotherapy, among other agents, by patients in the ITT population during follow-up was balanced between groups (neratinib, 25.2%; placebo, 28.2%).

“We think this analysis offers hope for a strategy of [tyrosine kinase inhibitors] in the early-stage setting, particularly with benefit seen in reducing CNS recurrence for highest-risk patients,” Tiffany A. Traina, MD, vice chair of oncology care and section head of the Triple-Negative Breast Cancer Clinical Research Program at Memorial Sloan Kettering Cancer Center, said in a virtual discussion of the updated ExteNET data. “[However], we may never know how extended-adjuvant neratinib performs following either pertuzumab [Perjeta] or T-DM1 [ado-trastuzumab emtansine; Kadcyla]-based regimens.”

REFERENCES
Tesetaxel Combo Improves PFS in Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer

by DARLENE DOBKOWSKI, MA

THE ADDITION OF TESETAXEL, a novel oral taxane, to a reduced dose of capecitabine demonstrated significant activity in patients with hormone receptor-positive, HER2-negative metastatic breast cancer that is resistant to chemotherapy, according to results from the phase 3 CONTESSA trial presented at the 2020 San Antonio Breast Cancer Symposium.

Specifically, investigators compared tesetaxel plus capecitabine with capecitabine alone in 685 patients with HER2-negative, hormone receptor-positive metastatic breast cancer. The treatment arms were well balanced with all patients having previously received a taxane, approximately 86% previously received an anthracycline, and approximately 50% had received a CDK4/6 inhibitor.

Results from CONTESSA (NCT03326674) demonstrated that at a median follow-up of 13.9 months, patients assigned to tesetaxel and capecitabine demonstrated a median progression-free survival (PFS) of 9.8 months, compared with 6.9 months in those assigned capecitabine alone, an improvement of 2.9 months (HR, 0.716; 95% CI, 0.573-0.895; P = .003).

“[Tesetaxel] is a new chemical entity that, unlike the other taxanes, such as paclitaxel and docetaxel, is not effluxed by the [P-glycoprotein] pump,” said lead author Joyce A. O’Shaughnessy, MD, a 2016 Giants of Cancer Care® award winner who is chair of breast cancer prevention research at the Breast Cancer Symposia.

Joyce A. O’Shaughnessy, MD

Tesetaxel plus or minus capecitabine had a manageable adverse event (AE) profile. Grade 3 or higher treatment-emergent AEs, which occurred in at least 5% of patients, were observed in more patients assigned to tesetaxel plus capecitabine compared with capecitabine alone, including diarrhea (13.4% vs 8.9%, respectively), neutropenia (71.2% vs 8.3%), fatigue (8.6% vs 4.5%), febrile neutropenia (12.8% vs 1.2%), leukopenia (10.1% vs 0.9%), hypokalemia (8.6% vs 2.7%), and anemia (8% vs 2.1%). In contrast, patients assigned capecitabine alone were more likely to develop hand-foot syndrome compared with those assigned tesetaxel plus capecitabine (6.8% vs 12.2%, respectively).

Several AEs resulting in treatment discontinuation each occurred in at least 1% of patients. Some events occurred more often in patients assigned to the combination therapy, such as neuropathy (3.6% vs 0.3%) and neutropenia or febrile neutropenia (4.2% vs 1.5%), whereas others were more common in patients assigned capecitabine alone including hand-foot syndrome (0.6% vs 2.1%) and diarrhea (0.9% vs 1.5%). Treatment discontinuation resulting from any AE was observed in 23.1% of patients assigned combination therapy compared with 11.9% of those assigned capecitabine alone.

Other AEs of note included grade 2 alopecia, which occurred in 8% of patients treated with the combination versus 0.3% with capecitabine alone, and grade 3 or greater neuropathy (5.9% vs 0.9%, respectively) and neuropathy (5.9% vs 0.9%).

“Tesetaxel plus a reduced dose of capecitabine is a potential new treatment option for patients with hormone receptor-positive, HER2-negative metastatic breast cancer,” O’Shaughnessy concluded.

REFERENCE

O’Shaughnessy J, Schwartzberg L, Piccart M, et al. Results from CONTESSA: a phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2+, hormone receptor + (HR+) metastatic breast cancer (MBC) who have previously received a taxane. Presented at: 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020; virtual. Abstract GS4-01.
U.S. News & World Report has recognized Hackensack Meridian John Theurer Cancer Center at Hackensack University Medical Center as the best cancer center in all of New Jersey. And as a member of one of just 16 NCI-designated cancer consortia, we have distinguished ourselves as New Jersey’s premier cancer center—offering nationally recognized cancer specialists, clinical trials and immunotherapy including CAR T-Cell.

To schedule a visit or a second opinion, call 551-996-5855 or visit HackensackMeridianHealth.org/GetCancerCareNow.
Trial Explores Preoperative Window for Amcenestrant Therapy in Early Breast Cancer

by DENISE MYSHKO

INVESTIGATORS ARE SEEKING TO determine whether amcenestrant (SAR439859), an investigational oral endocrine therapy, can generate meaningful antitumor activity when administered as short-term preoperative therapy to postmenopausal patients with newly diagnosed early breast cancer.

The phase 2 AMEERA-4 trial (NCT04191382) is testing 2 dose levels of amcenestrant versus letrozole given for 14 days to patients with estrogen receptor (ER)-positive, HER2-negative localized breast cancer who are candidates for breast conserving therapy or upfront mastectomy.

The study will measure the impact of the short course of endocrine therapy on Ki-67, a protein biomarker of cellular proliferation that has been shown to be a prognostic indicator of survival and recurrence in patients with early breast cancer, with higher levels associated with worse outcomes.

Ki-67 expression has been correlated with poor cancer-specific survival at a cutoff point greater than 14% of tumor nuclei.

AMEERA-4 is a “window of opportunity study,” a validated strategy for rapid exploration of proof-of-concept treatment approaches, investigators said in a poster presentation at the 2020 American Society of Clinical Oncology Virtual Scientific Program.

The trial’s goals include determining the best dosage for further study of amcenestrant in this clinical setting, said principal investigator Mario Campone, MD, a medical oncologist at the Institut de Cancérologie de l’Ouest, René Gauducheau, in St Herblain, France.

“Some clinical trials have demonstrated that when you have a decrease in Ki-67 after 2 weeks you have a better outcome compared with the patients who do not have a decrease in this surrogate marker,” he said in an interview with OncologyLive.

Amcenestrant is a selective ER degrader (SERD), a class of drugs that works by serving as a competitive antagonist to the ER, inducing conformational changes that lead to degradation of the receptors. In preclinical studies, the agent has demonstrated antitumor efficacy and regression in ER-positive breast cancer models.

Further, amcenestrant can be administered as an oral therapy because of its favorable pharmacokinetic profile, as opposed to fulvestrant (Faslodex), a SERD that must be given via intramuscular injection because of pharmacokinetic limitations.

AMEERA-4 STUDY DETAILS

AMEERA-4, an international, open-label study, was initiated in December 2019 and is being conducted at 16 active sites with 34 planned sites, Campone said.

Participants are being randomized 1:1:1 to receive daily amcenestrant at 400 mg, daily amcenestrant at 200 mg, or daily letrozole at 2.5 mg for 14 days, with the...
last dose administered on the day before surgery. Biopsies are performed at baseline and during surgery (FIGURE).1,4

The primary end point is a change in Ki-67 expression measured by immunohistochemistry after a 14-day treatment period compared with baseline levels. Secondary end points include the proportion of patients with relative decrease from baseline in Ki-67 expression of 50% or more, change in ER expression compared with baseline, and safety and tolerability.

Efficacy will be assessed via pathologic complete response (pCR), which is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen and axillary nodes after treatment. ECOG performance status response will be measured after the 14-day treatment based on breast tumor shrinkage and pCR. Additionally, a preoperative endocrine prognostic index derived from pathologic tumor and node stages, Ki-67 levels, and ER status of the surgical specimen will be assessed after the 14-day treatment period.

Investigators are seeking to recruit 126 patients for the study. So far, 14 patients have been enrolled, and the study could be completed sometime this year, with data analysis projected for 2022, Campone said.

After completion of the AMEERA-4 study, Sanofi, the agent’s developer, plans to initiate a pivotal clinical trial to study amcenestrant in early breast cancer.7 AMEERA-6 will be a registrational study with invasive disease-free survival as the primary end point. This study will be supported in part by data generated from AMEERA-4, which is expected in to be available in 2021, according to a Sanofi spokesperson. AMEERA-6 is expected to begin recruiting patients by the end of 2021.

**EARLY SIGNS OF EFFICACY**

The use of amcenestrant as monotherapy has shown encouraging signals in the ongoing phase 1/2 AMEERA-1 trial (NCT03284957). In interim results reported at the 2020 San Antonio Breast Cancer Symposium, amcenestrant monotherapy elicited antitumor activity in heavily pretreated, postmenopausal women with advanced or metastatic ER-positive breast cancer.8

Results showed that the objective response rate (ORR) was 8.5% with amcenestrant with a clinical benefit rate (CBR) of 33.9% among pooled results from 59 patients who received amcenestrant at 150 mg or more daily. In a cohort of 33 patients who had received 3 or fewer prior lines of therapy in the metastatic setting, the ORR was 15.2% and the CBR was 42.4%. Moreover, in a subgroup of 14 patients who did not receive prior CDK4/6 inhibitors, mTOR inhibitors, or fulvestrant, the ORR was 21.4% and the CBR was 64.3%.8

In AMEERA-1, which is a first-in-human study, investigators are evaluating the safety and efficacy of amcenestrant as a single agent and in combination with targeted therapies in patients with ER-positive, HER2-negative metastatic breast cancer. In part A of the trial, which was the dose-escalation phase, investigators evaluated amcenestrant at once-daily doses ranging from 20 mg to 600 mg. In part B, which was the dose-expansion phase, the recommended dose for amcenestrant as monotherapy was determined to be 400 mg once daily.

Amcenestrant was found to have a favorable safety profile with 62.9% of patients experiencing treatment-related adverse events (TRAEs), none of which were grade 3 or higher. The most common (25%) TRAEs in the pooled population of patients who were treated with amcenestrant at the 150-mg or higher daily dose included hot flush (16.1%), constipation (9.7%), arthralgia (9.7%), decreased appetite (8.1%), vomiting (8.1%), diarrhea (8.1%), nausea (8.1%), and fatigue (6.5%).8

Pivotal results are expected in the first half of 2021, according to Sanofi. Amcenestrant as a monotherapy may be available as a second- and third-line treatment for patients with metastatic breast cancer in 2022, the company said.7

**LARGE TRIALS IN PROGRESS**

Amcenestrant monotherapy is also being evaluated versus physician’s choice of therapy in the open label, phase 2 trial AMEERA-3 trial (NCT04059484), which will enroll 372 patients. The control treatment involves choosing monotherapy from a list of agents with different mechanisms of action: anastrozole, letrozole, or exemestane, which are aromatase inhibitors; tamoxifen, a selective estrogen receptor modulator; or fulvestrant. The primary end point is progression-free survival (PFS). Secondary end points include OS, ORR, disease control rate, CBR, and duration of response (DOR).9

Another study, AMEERA-5 (NCT04478266), is testing amcenestrant in combination with palbociclib (Ibrance), a CDK4/6 inhibitor, versus letrozole plus palbociclib as a first-line therapy for patients with ER-positive, HER2-negative locoregional or metastatic breast cancer. The study, which aims to recruit 810 patients, has a primary end point of PFS and secondary end points of OS, ORR, DOR, and CBR.10

Additionally, the Quantum Leap Healthcare Collaborative announced in June 2020 that amcenestrant was selected to be part of a new I-SPY 2 study arm.

The study, known as the I-SPY 2 Endocrine Optimization Protocol (EOP), is focused on patients with molecularly low-risk, clinically high-risk, hormone receptor-positive, HER2-negative clinical stage II or III invasive breast cancer. Amcenestrant will be tested as a monotherapy and in combination with up to 3 other agents.11

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

“Some clinical trials have demonstrated that when you have a decrease in Ki-67 after 2 weeks you have a better outcome.”

—MARIO CAMPONE, MD

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

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**BREAST CANCER | Clinical Trial In Focus**

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**FIGURE**

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New Targeted Treatment Helps Delay ALK+ mNSCLC Progression

BRAIN METASTASES ARE A COMMON PRESENTATION in non-small cell lung cancer (NSCLC), particularly in patients with the anaplastic lymphoma kinase (ALK) gene rearrangement. In fact, approximately one third of patients with ALK-positive (ALK+) metastatic NSCLC (mNSCLC) will present brain metastases at the time of diagnosis.¹

The occurrence of brain metastases further complicates the treatment of these patients and puts them at risk for serious side effects and a shorter life expectancy.² However, the discovery of targeted agents known as ALK inhibitors has dramatically changed the treatment of ALK+ mNSCLC.³ Effective targeted therapies have provided patients with the potential to achieve high overall response rates and remain progression-free for longer periods of time.³ And the landscape has continued to evolve – with a focus on advancing options available for newly diagnosed patients in the first-line setting.

An Evolving Treatment Landscape
In less than 10 years, several different ALK inhibitors have come to market. Crizotinib, the first approved ALK inhibitor, quickly became the standard of care for patients, but further research uncovered that it had poor penetration in the brain, which posed a problem for the majority of patients who develop brain metastases during the course of their disease.⁴ Therapies demonstrating intracranial efficacy – in addition to overall efficacy – were needed to effectively address the unique needs of patients in this population. This led to the rise of second-generation ALK inhibitors, which have more effectively delayed progression and achieved higher response rates.

Today, several second-generation ALK inhibitors are available for patients in the first-line setting. While each of the approved ALK inhibitors have shown to be effective, it’s important to have multiple treatment options available to help optimize treatment sequencing. Case in point, treatment resistance is a common occurrence among patients that limits long-term effectiveness of targeted therapies.⁴ Many patients with ALK+ mNSCLC develop resistance after deriving initial benefit from a targeted therapy through a variety of mecha-
nisms. To improve outcomes in the treatment of ALK+ mNSCLC, introducing new therapies that may help overcome ALK inhibitor resistance and provide another option for patients and healthcare providers should be a continued priority.

The Role of ALUNBRIG in the ALK+ mNSCLC Treatment Landscape
ALUNBRIG® (brigatinib) is a second-generation ALK inhibitor that was recently approved by the U.S. Food & Drug Administration (FDA) for adult patients with ALK+ mNSCLC as detected by an FDA-approved test. The approval was based on results from the international, open-label, multicenter, Phase 3 ALTA 1L trial, which compared the efficacy and safety of ALUNBRIG with crizotinib in 275 adult patients with ALK+ mNSCLC, who had not previously received prior treatment with an ALK inhibitor.

Patients were randomized to receive ALUNBRIG 180 mg orally once daily with a 7-day lead-in at 90 mg once daily (n=137) or crizotinib at 250 mg orally twice daily (n=138). The primary endpoint was progression-free survival (PFS) per RECIST v1.1 as assessed by a blinded independent review committee (BIRC).

Long-term data from the trial showed that ALUNBRIG yielded superior overall and intracranial efficacy outcomes compared to crizotinib. Importantly, newly diagnosed patients treated with ALUNBRIG benefited regardless of the presence or absence of brain metastases at baseline.

- In the intent-to-treat (ITT) population, the BIRC-assessed median PFS was 24.0 months (95% CI: 18.5–NE) for ALUNBRIG and 11.0 months (95% CI: 9.2–12.9) for crizotinib.
- Confirmed overall response rate (ORR) was 74% (95% CI: 66–81) for ALUNBRIG and 62% (95% CI: 53–70) for crizotinib as assessed by a BIRC.
- The median duration of response (DoR) in confirmed responders was not reached (95% CI: 19.4–NE) with ALUNBRIG and was 13.8 months (95% CI: 9.3–20.8) with crizotinib as assessed by a BIRC.

Additionally, ALUNBRIG demonstrated robust and durable responses in the brain, with patients with baseline brain metastases treated with ALUNBRIG yielding superior efficacy compared to crizotinib, as assessed by a BIRC.

- Confirmed intracranial ORR for patients with measurable brain metastases at baseline was 78% (95% CI: 52–94) for patients treated with ALUNBRIG (n=14/18) and 26% (95% CI: 10–48) for patients treated with crizotinib (n=6/23).
- The proportion of patients who demonstrated an intracranial DoR ≥24 months was 64% in the ALUNBRIG arm and was not reached in the crizotinib arm.

The safety profile of ALUNBRIG in the ALTA 1L trial was generally consistent with previous trials. Serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions other than disease progression were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions other than disease progression occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%). The most common adverse reactions in the ALTA 1L trial (≥10%) with ALUNBRIG were diarrhea (53%), rash (40%), cough (35%), hypertension (32%), fatigue (32%), nausea (30%), myalgia (28%), dyspnea (25%), abdominal pain (24%), and headache (22%).

Other Considerations in Making Treatment Decisions
In addition to treatment efficacy and safety considerations, it’s important for healthcare providers to understand how a therapy may affect ALK+ mNSCLC patients’ everyday lives when determining the best treatment option. This is particularly important for patients who may be on treatment for several years.

Unlike the general NSCLC population, ALK+ mNSCLC patients are often younger, with a median age of between 50 and 55 years old. For many of these patients, a treatment option that allows them the ability to maintain a sense of normalcy is crucial. ALUNBRIG’s one pill a day administration can have a less significant impact on a patient’s daily routine compared to other regimens. During times like these, the benefits of an oral administration are particularly relevant – given the risk involved with immuno-compromised patients traveling and attending hospital visits due to the COVID-19 pandemic.

In summary, remarkable progress has been made in the treatment of ALK+ mNSCLC patients, and the field continues to grow at a rapid pace. We look forward to working with industry and academic colleagues to spearhead continued progress that will help delay disease progression, so patients can continue on with their lives for as long as possible, with as little disruption as possible.
**ALUNBRIG IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Interstitial Lung Disease (ILD)/Pneumonitis:** Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), ILD/pneumonitis occurred in 5.1% of patients receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients. In Trial ALTA, ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90 → 180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early within 9 days of initiation of ALUNBRIG (median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

**Hypertension:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients. In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90 → 180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1, resume ALUNBRIG at the same dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

**Bradycardia:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%). In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90 → 180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

**Visual Disturbance:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG. In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90 → 180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90 → 180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

**Creatine Phosphokinase (CPK) Elevation:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients. In ALTA, CPK elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg → 180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90 → 180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90 → 180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation with Grade 2 or higher muscle pain or weakness. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

**Pancreatic Enzyme Elevation:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients. In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90 → 180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90 → 180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90 → 180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90 → 180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

**Hyperglycemia:** In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 7.5% of patients.
In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

**Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise females of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

**ADVERSE REACTIONS**

In ALTA 1L, serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions other than disease progression were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions other than disease progression occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%). In ALTA, serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90 → 180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90 → 180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90 → 180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each). The most common adverse reactions ≥25% with ALUNBRIG were diarrhea (49%), fatigue (39%), nausea (39%), rash (38%), cough (37%), myalgia (34%), headache (31%), hypertension (31%), vomiting (27%), and dyspnea (26%).

**DRUG INTERACTIONS**

**CYP3A Inhibitors:** Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG.

**CYP3A Inducers:** Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, increase the dose of ALUNBRIG.

**CYP3A Substrates:** Coadministration of ALUNBRIG with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

**Lactation:** There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.

**Females and Males of Reproductive Potential:**

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG.

Contraception: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

**Pediatric Use:** The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

**Geriatric Use:** Of the 359 patients enrolled in the ALTA 1L ALUNBRIG arm and in ALTA, 26.7% were 65 and older and 7.5% were 75 and older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

**Hepatic or Renal Impairment:** No dose adjustment is recommended for patients with mild or moderate hepatic impairment or mild or moderate renal impairment. Reduce the dose of ALUNBRIG for patients with severe hepatic impairment or severe renal impairment.

Please see the full U.S. Prescribing Information for ALUNBRIG at www.ALUNBRIG.com

**REFERENCES**

Subcutaneous Daratumumab Improves PFS in Myeloma

by KRISTIE L. KAHL

THE ADDITION OF SUBCUTANEOUS daratumumab and hyaluronidase-fihj (Darzalex Faspro) to pomalidomide (Pomalyst) and dexamethasone (DPd) significantly reduced the risk of progression or death by 37% compared with pomalidomide and dexamethasone (Pd) in patients with relapsed/refractory multiple myeloma (RRMM) who had received at least 1 prior line of therapy, according to results from the phase 3 APOLLO study.1

Moreover, the combination achieved a significantly deeper response compared with pomalidomide monotherapy, including a higher complete response rate (24.5% vs 3.9%, respectively) and minimal residual disease (MRD) negativity (9% vs 2%; P = .0102), supporting the use of the subcutaneous formulation as a replacement for intravenous daratumumab (Darzalex).

“Daratumumab is a CD38 monoclonal antibody with multiple modes of action, which have shown not only single-agent activity, but also, whenever this drug was combined with other standard regimens—either in a lab setting or in the frontline setting—there was a significant improvement in progression-free survival and also in overall survival,” Meletios A. Dimopoulos, MD, said during a press briefing at the 62nd American Society of Hematology Annual Meeting & Exposition in December 2020. Dimopoulos is professor and chairman of the Department of Clinical Therapeutics at the National and Kapodistrian University of Athens School of Medicine in Greece.

Recent study results have found that the subcutaneous formulation of daratumumab is similar in efficacy and safety compared with the intravenous formulation. In addition, it has a statistically significant reduction in infusion-related reaction rates and a considerably shorter administration time of 5 minutes.

The formulation of daratumumab and hyaluronidase-fihj was approved by the FDA in May 2020 across several indications for daratumumab; however, the approved indications do not include the formulation as a replacement for daratumumab in combination with pomalidomide and dexamethasone.2

In the open-label, multicenter, phase 3 APOLLO study (NCT03180736), investigators compared subcutaneous daratumumab plus Pd with Pd alone in 304 patients with RRMM who had received at least 1 prior line of therapy, including lenalidomide (Revlimid) or a proteasome inhibitor.

To be eligible for the trial, patients with only 1 prior line of therapy were required to be refractory to lenalidomide. Prior treatment with an anti-CD38 agent or pomalidomide was not permitted.

All patients received treatment on 28-day cycles until progressive disease or unacceptable toxicity. Patients were randomized 1:1 to received DPd (n = 153) or Pd alone (n = 151). The DPd regimen consisted of 1800 mg subcutaneous daratumumab every week for cycles 1 and 2, biweekly from cycles 3 to 6, and every 4 weeks starting at cycle 7; 4 mg pomalidomide from days 1 to 21; and 40 mg dexamethasone on days 1, 8, 15, and 22. Median duration of subcutaneous administration was 5 minutes (range, 1-22).1

Posttreatment follow-up was conducted every 4 weeks for patients who discontinued treatment. Survival follow-up was conducted every 12 weeks following progressive disease or the start of subsequent therapy.

Progression-free survival (PFS) served as the primary end point. Secondary end points included overall response rate, rates of very good partial response (VGPR) or better and complete response or better, MRD negativity rate, overall survival, time to response, duration of response, time-to-next therapy, safety, and health-related quality of life.

At baseline, 79.6% of patients were refractory to lenalidomide, 48.0% were refractory to a proteasome inhibitor, and 42.4% were refractory to both. Median duration of treatment was 11.5 months with DPd, compared with 6.6 months with Pd.

Compared with Pd alone, DPd demonstrated superior PFS (HR, 0.63; 95% CI, 0.47-0.85; P = .0018). Specifically, the median PFS was 12.4 months for patients treated with DPd compared with 6.9 months in patients treated with Pd alone. Moreover, the median PFS among patients treated with DPd who were refractory to lenalidomide was 9.9 months compared with 6.5 months for those who were not.

At a median follow-up of 16.9 months, 99 patients (33%) had died. The risk for death was decreased by 9% with DPd (HR, 0.91; 95% CI, 0.61-1.35); however, survival data are immature and follow-up is ongoing.

The overall response rate was higher in the DPd group compared with the Pd group (69% vs 46%, respectively; OR, 2.68; 95% CI, 1.65-4.35; P < .0001), including VGPR rates (51.0% vs 19.6%).

The safety profile of DPd was consistent with its known profile. The most common grade 3/4 adverse effects (AEs) in patients treated with DPd versus Pd were neutropenia (68% vs 51%, respectively), leukopenia (17% vs 5%), lymphopenia (12% vs 3%), febrile neutropenia (9% vs 3%), and pneumonia (13% vs 7%). Rates of study treatment discontinuation due to treatment-emergent AEs were similar for both arms (2% vs 3%, respectively). The most common reason for treatment discontinuation was progressive disease. The rate of infusion-related reaction rates with the subcutaneous formulation appeared low (grade 1/2, 6%), and only 2% of patients had a local injection site reaction.

“The infusion-related reaction rate was low and administration duration was short, thus increasing convenience for patients and decreasing treatment burden,” Dimopoulos said. “DPd is an effective and convenient treatment for patients with relapsed/refractory multiple myeloma who have received at least 1 prior line of therapy, including lenalidomide and the proteasome inhibitor.”

For a full list of references, see the article at https://bit.ly/35e7VlH.
OVERVIEW

The 17th Annual International Symposium on Melanoma and Other Cutaneous Malignancies® is a single-day educational conference designed to examine current and emerging treatments in melanoma, basal cell carcinoma, squamous cell carcinoma, and other skin-related cancers.

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The fast-paced and interactive nature of this symposium will provide:

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- The latest research to improve your clinical practice
- Evidence-based answers from the dynamic and interactive Medical Crossfire® discussions

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- Develop action plans to improve the treatment of your patients with skin-related cancers
- Learn the current best practices for managing adverse events of current and novel therapies used to treat melanoma and other cutaneous tumors
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REGISTRATION FEES

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USING REAL-WORLD DATA from more than 4000 patients with common cancers, a algorithm was able to detect variations in care that, if reduced, could result in a median savings of $26,773 per patient, according to recent study findings.  

Investigators said the COTA Nodal Address (CNA) system identified a wide variation in treatment provided to patients with breast, colorectal (CRC), or lung cancers, with less than 10% receiving care based on the same pathway. Costs of care for the same CNA ranged from $16,000 to $88,000 for patients with breast cancer, $25,000 to $222,000 for those with CRC, and $44,000 to $424,000 for those with lung cancer.  

The findings have implications for value-based oncology care models, investigators said in an article published in the Journal of Precision Medicine.  

Studies have noted that at least 20% of the nearly $3 trillion spent annually on cancer care in the United States “fails to enhance clinical outcomes and may be considered waste,” they said.  

“Everyone always assumed there was this variation, but no one has characterized this so precisely up front,” lead author Andrew L. Pecora, MD, FACP, CPE, said in an interview. “What we found is that for people who were seemingly identical, there are a whole lot of choices being made with a huge difference in total cost of care and no difference in outcomes, despite their being identical-type patients.”  

Pecora is founder and executive chairman of COTA Inc, a health care analytics company that developed CNA, a digital classification system that groups patients with similar characteristics. It incorporates clinical and disease-specific elements that influence treatment choice and clinical outcomes, including cancer type, phenotype, and progression of disease, as well as patient characteristics such as age, sex, and cancer stage.  

“The COTA Nodal Address is a numeric representation of an individual patient that takes into account everything that is relevant about them, the disease they have, where they are in the history of their disease, and any and all other factors that might influence a treatment choice for an outcome. It is like your own personal bar code,” Pecora said.  

The CNA model, Pecora added, aims to sort similar patients into groups for comparison. “When you get down to that level of specificity, you can look at seemingly identical patients medically, what care choices were made for them, and what the clinical outcomes and costs were,” he said.  

The system allows for a much finer grain of understanding of categories of patients within each diagnosis so investigators can study how patients with similar conditions are being treated, said Donald M. Berwick, MD, MPP, a coauthor on the paper.  

“The idea was to use modern computer technology to help understand the profile of different lines of care being given to patients [with cancer] within a certain subset of cancers,” said Berwick, a lecturer on health care policy at Harvard Medical School in Boston, Massachusetts; president emeritus and senior fellow for the Institute for Healthcare Improvement; and former administrator of the Centers for Medicare & Medicaid Services.  

STUDY FINDINGS  

In this retrospective analysis, investigators used CNA to review the health records of 4893 patients treated from January 2013 to January 2016 at Hackensack Meridian Health institutions, which include 16 hospitals in New Jersey. Of these patients, 82% (n = 4032) had enough information in their
The analysis did not evaluate outcomes for the care pathways, although the CNA system can analyze that as well. Investigators noted that most of the care choices observed in this analysis were part of the current National Comprehensive Cancer Network guidelines and would be considered clinically appropriate. The study authors said further analysis of the CNA model is needed to identify and explain variance in care.

The study findings come at a time of growing adoption of clinical pathway systems. The State of Cancer Care in America 2017 report, from the American Society of Clinical Oncology (ASCO), documented a 42% increase from 2014 to 2016 in practices reporting compliance with a pathway program. ASCO estimates that about 60 individual health insurance plans in the United States are implementing oncology pathways, with more than 170 million individuals covered by those plans.

ASCO formed a task force on pathways in January 2015, and the organization has since developed recommendations and published criteria defining the elements of a high-quality pathway.

“One of the benefits of the COTA approach is to come up with smarter agreed-upon standards,” Berwick said. “If the evidence accumulates [and shows] that a particular approach produces the best outcomes, perhaps that gives us a new opportunity for payers to come together and not create such chaos for oncologists with multiple pathways.”

Investigators argue that the CNA model can encourage value-based cancer care, and they will continue to evaluate whether the approach can form the backbone of a bundled payment model. The Oncology Care Model is one such alternative payment model, which the Centers for Medicare & Medicaid Services implemented in 2016. The eventual goal, the investigators said, is to use the CNA model to support value-based oncology care models and deliver more individualized care. “There are all these pathways and guidelines out there, and for all these seemingly identical

patients, many different care choices are being made,” Pecora said. “The question is: Why is that happening. With the COTA Nodal Address, we believe we can largely eliminate that variation.”

Pecora said a future study is planned to analyze these variations prospectively. “We want to give people the CNA insight before they make their treatment decisions to determine whether that can reduce variation in treatment choice, maintain clinical outcomes, and reduce total cost of care,” he noted.

Berwick pointed out that this current analysis was conducted on just 3 cancer types. “There are other cancers and even other conditions beyond cancer that could be subject to the same kind of analysis. Based on what COTA is seeing, it will invite further inquiry about which patterns of treatment produce the best result. That is work that lies ahead,” he said.

REFERENCES
MANY PHYSICIANS ARE LOOKING to hire a telehealth service company now, as they try to treat patients during the coronavirus disease 2019 (COVID-19) pandemic. But even though practices want to get their telehealth program started quickly, the due diligence process should not be rushed. There are criteria every physician should use to evaluate potential vendors, and many organizations are putting out guides to help with this process. The American Medical Association recently released an expanded telehealth guide that describes the criteria physicians should use when selecting a vendor, including:

Understand basic business information
- What is the company’s organizational overview?
- How long have they been around?
- What is their funding source? Are they financially stable?
- Who are they affiliated with?
- Do they have any notable customers?

Cost and prices
- How will this company impact your program return on investment?
- How much does the product cost?
- What is their business model?
- What are the details on reimbursement rates, risk sharing, and more?
- What is the cost, process, and timeline associated with integration and any product updates?

Is it a fit?
- How well do they know you?
- Do they have expertise in offering telehealth to your specialty?
- Do they have knowledge of federal and private payer requirements?
- Do they know the laws and regulations in your state?

Technology needs
- Does their tech match your needs?
- Can they integrate with your IT landscape, particularly your electronic health records?
- Can their system capture data important to both the care team and the patient?
- What are their customization capabilities?
- Can patients access their data?

Cybersecurity and privacy
- Does the vendor have a secure system?
- Do they comply with HIPAA rules?
- Will they sign a business associate agreement with your practice?
- What is their liability structure for managing security breaches?
- Do they comply with local regulations, such as state medical board rules?

System usability
- How well does their system work?
- How easy is their system to use for clinicians and patients?
- Does it provide engagement metrics?
- How well do the dashboard and workflow systems work?
- How easy is the billing system?

Vendor support services
- How is their customer service?
- How much initial training do they provide?
- How much support do they provide beyond initial training? Patient education? Project management? Data analysis?
- What is their technical support process like?
- Do you have access to existing templates and procedure examples?

Clinical validation
- Is their system credible clinically?
- Do they have documentation that supports improving clinical outcomes?
- Is there any published peer-reviewed research of their system?

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For women with HR+, HER2- MBC* who have visceral disease† or primary ET resistance‡

Survival doesn’t have to be at higher risk1§

Visceral disease† and primary ET resistance‡ are associated with higher risk.1,4

*With disease progression following ET.
†Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement.5
‡Primary resistance was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC.6,7
§Patients with higher-risk disease, defined as the presence of visceral disease or primary ET resistance, were included in the MONARCH 2 clinical trial.8 ET=endocrine therapy; HER2=human epidermal growth factor receptor 2–negative; HR+=hormone receptor–positive; MBC=metastatic breast cancer.

Indication
Verzenio® (abemaciclib) is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced or metastatic breast cancer (MBC)6:

• In combination with fulvestrant for women with disease progression following endocrine therapy

Important Safety Information
Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
In HR+, HER2- MBC*

Verzenio is the only CDK4 & 6 inhibitor to achieve significant overall survival improvement in combination with fulvestrant regardless of menopausal status

**OS in ITT Population**

- Results are based on a prespecified interim analysis and are considered definitive.
- The percentage of deaths at the time of analysis was 47.3% (n=211) and 57.0% (n=127) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively.
- Primary endpoint of median PFS was met: 16.4 months (95% CI: 14.4-19.3) median PFS with Verzenio plus fulvestrant vs 9.3 months (95% CI: 7.4-12.7) with fulvestrant alone (HR=0.553; 95% CI: 0.449-0.681; P<0.0001)
- The percentage of PFS events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively.

**Study Design**

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2- MBC who progressed on or after ET. Pre/perimenopausal women (17%) were rendered postmenopausal prior to the study. Patients had received no chemotherapy and no more than 1 prior ET in the metastatic setting. Patients were randomized 2:1 to Verzenio plus fulvestrant (n=446) or placebo plus fulvestrant (n=223). Verzenio and placebo were dosed PO BID on a continuous dosing schedule until disease progression or unacceptable toxicity. 500 mg fulvestrant was administered by IM injection on days 1, 15, and 29 of the first month and once monthly thereafter. The primary endpoint was PFS. Key secondary endpoints were ORR, OS, and DoR.

**Important Safety Information (cont’d)**

Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

*With disease progression following ET.

BID=twice daily; CDK4 & 6=cyclin-dependent kinases 4 and 6; DoR=duration of response; IM=intramuscular; ITT=intent-to-treat; mOS=median overall survival; ORR=objective response rate; PFS=progression-free survival; PO=orally.
In HR+, HER2- MBC*

Even women with worse prognoses achieved survival outcomes consistent with the overall study population¹

**WOMEN WITH VISCERAL DISEASE† HAD**

8.1 months longer mOS¹

40.3 months mOS with Verzenio plus fulvestrant (n=245) vs 32.2 months mOS with fulvestrant alone (n=128).

HR=0.675 (95% CI: 0.511-0.891)

**WOMEN WITH PRIMARY ET RESISTANCE‡ HAD**

7.2 months longer mOS¹

38.7 months mOS with Verzenio plus fulvestrant (n=112) vs 31.5 months mOS with fulvestrant alone (n=60).

HR=0.686 (95% CI: 0.451-1.043)

- Preplanned subgroup analyses of PFS and OS were performed for stratification factors of disease site (including visceral disease) and endocrine resistance (including primary ET resistance). Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups¹

*With disease progression following ET.
†Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement.⁵
‡Primary resistance was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC.⁶,⁷

**Important Safety Information (cont’d)**

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.

Grade ≥3 increases in alanine aminotransferase (ALT) (6% versus 2%) and aspartate aminotransferase (AST) (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 2.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential hepatotoxicity, monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo.

Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause fetal harm when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The most common adverse reactions (all grades, ≥10%) observed in MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 2 were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inhibitors and consider alternative agents. Coadministration of strong or moderate CYP3A inhibitors decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced exposure.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with severe renal impairment (Clcr<30 mL/min), end stage renal disease, or in patients on dialysis is unknown. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (Clcr ≥30–89 mL/min).

Important Safety Information (cont’d)

Please see Brief Summary of full Prescribing Information for Verzenio on the following pages. AL HCP ISI_M2_23OCT2019

*With disease progression following ET.
†Patients with higher-risk disease, defined as the presence of visceral disease or primary ET resistance, were included in the MONARCH 2 clinical trial.

Verzenio® (abemaciclib) tablets, for oral use

Initial U.S. Approval: 2017

Brief Summary: Consult the package insert for complete prescribing information.

Indications and Usage
Verzenio® (abemaciclib) is indicated:
- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

Contraindications:
None.

Warnings and Precautions
Diarrhea
Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2, and 23% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2, and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection. Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1. Instruct patients that at the first sign of loose stools, they should start anti-diarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further reductions and appropriate follow up. For Grade 4 or 5 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤ Grade 1, and then resume Verzenio at the next lower dose.

Neutropenia
Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2, and 37% of patients receiving Verzenio alone in MONARCH 1. Grade 3 neutropenia occurred in 1% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 3% of patients receiving Verzenio plus fulvestrant in MONARCH 2, and in 27% of patients receiving Verzenio in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days. Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Fibrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2, inform patients to promptly report any episodes of fever to their healthcare provider.

Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, or fatal lung disease (ILD) and/or pneumonitis can occur in patients treated with Verzenio and other CDK 4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended for patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis.

Hepatotoxicity
In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the Verzenio and placebo arms, respectively. In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms, respectively.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 ALT increased, median time to onset was 61 days, and median time to resolution was 14 days. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous Thromboembolism
In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embry-Fetal Toxicity
Based on findings from animal studies and the mechanism of action, Verzenio can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose.

Adverse Reactions
Clinical Studies 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.

MONARCH 2: Verzenio in Combination with Fulvestrant
Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of Verzenio (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to Verzenio in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of Verzenio plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving Verzenio plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving Verzenio plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. Verzenio dose reductions due to diarrhea of any grade occurred in 13% of patients receiving Verzenio plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. Verzenio dose reductions due to neutropenia of any grade occurred in 10% of patients receiving Verzenio plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving Verzenio plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving Verzenio plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of Verzenio plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving Verzenio plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) patient death due to other causes.

The most common adverse reactions reported (≥20%) in the Verzenio arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 3). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, and anemia.
fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior (GFR), which are not based on creatinine, may be considered to determine whether within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

Table 1: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>VERZENIO plus Fulvestrant (N=223)</th>
<th>Placebo plus Fulvestrant (N=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>86 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>45 (3)</td>
</tr>
<tr>
<td>Abdominal Paina</td>
<td>35 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15 (1)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Infectional</td>
<td>43 (5)</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>46 (24)</td>
</tr>
<tr>
<td>Anemia</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Leukopeniaα</td>
<td>26 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (2)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>46 (3)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>12 (0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (1)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27 (4)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15 (0)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>16 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (1)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (0)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10 (1)</td>
</tr>
</tbody>
</table>
| Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness. Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis. Includes neutropenia, neutrophil count decreased. Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased. Includes leukopenia, white blood cell count decreased. Includes platelet count decreased, thrombocytopenia. Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 2: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>VERZENIO plus Fulvestrant (N=223)</th>
<th>Placebo plus Fulvestrant (N=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine Increased</strong></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>30 (5)</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>90 (23)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>87 (29)</td>
</tr>
<tr>
<td>Anemia</td>
<td>84 (3)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>53 (1)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>41 (4)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>37 (4)</td>
</tr>
</tbody>
</table>

Creatinine Increased
Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

Table 3: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>VERZENIO plus Fulvestrant (N=223)</th>
<th>Placebo plus Fulvestrant (N=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Interactions</strong></td>
<td></td>
</tr>
</tbody>
</table>

Effect of Other Drugs on VERZENIO

CYP3A Inhibitors
Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole
Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors
In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.

Moderate CYP3A Inhibitors
With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements, if necessary.

Strong and Moderate CYP3A Inducers
Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (see Data). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data
In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses >4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Lactation

Risk Summary
There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing
Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females
VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males
Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.
Pediatric Use
The safety and effectiveness of VERZENIO have not been established in pediatric patients.

Geriatric Use
Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment
No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment
No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

OVERDOSAGE
There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.
Additional information can be found at www.verzenio.com.
Eli Lilly and Company, Indianapolis, IN 46285, USA
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AL HCP BS_M2 28JAN2020
28-Gene Score May Predict Distant Metastatic Recurrence in Advanced Head and Neck Cancers

by ALLEN MO, MD, PhD

HEAD AND NECK CANCERS represent a wide-ranging category of diseases, and the sixth most common cancer in the United States. More than two-thirds of patients who receive an initial diagnosis of head and neck cancer already have a malignancy that has progressed to an advanced stage requiring a multimodality approach to care that includes radiation and chemotherapy. Although the ability to treat head and neck cancer has certainly improved over the years, a significant percentage of patients experience recurrent disease after initial treatment. The challenge and promise in advancing treatment in head and neck cancer lies in a better characterization of at-risk patients and understanding of how cancers recur.

Multiple clinical risk factors have been used for their potential prognostic value of head and neck cancers; however, their use has not been clearly defined in identifying mechanisms of treatment resistance for the subset of patients who fail initial therapy. Moreover, the promise of genetic-based risk stratification in the era of parallel sequencing has yet to be realized.

At its core, cancer is a genetic disease. Every cell in the body is controlled by a series of instructions encoded in genes. Occasionally, mutations override the normal safety checks and lead to uncontrolled cell growth and proliferation, which in turn leads to cancer. By harnessing genetic differences, our team of investigators at Montefiore Health System and the National Cancer Institute–designated Albert Einstein Cancer Center in the Bronx, New York, developed a prognostic genetic risk score to identify which patients are at highest risk for disease recurrence.

The development of a genomic prognostic tool resulted from a collaboration with a team that comprised Chandan Guha, PhD, MBBS, director of the Albert Einstein College of Medicine Institute for Onco-Physics, and a professor and vice chair of the Department of Radiation Oncology; Michael B. Prystowsky, MD, PhD, a professor and chair of the Department of Pathology; and Thomas Ow, MD, an associate professor of otolarhinolaryngology and pathology. To assess which patients with locally advanced disease were at greatest risk, the investigators identified cases from The Cancer Genome Atlas, a landmark cancer genomics program that molecularly characterized more than 20,000 primary cancers, including cancers of the head and neck. Twenty-four cases with distant metastases—tumor cells which have broken away from the primary tumor and traveled to other areas of the body—and 48 matched nonmetastatic controls were selected. A total of 1100 genes were differentially expressed, with primary changes in epithelial-stromal remodeling, and cytokine-immune interactions on functional pathway analysis.

The team developed a genetic signature based on patients with reported distant metastatic treatment failure and used a Least Absolute Shrinkage and Selection Operator regression analysis to refine a clinically applicable 28-gene prognostic score.

The score was validated in an internal prospective multidisciplinary study that comprised more than 120 patients treated at Montefiore. Results showed that patients with a high-risk score had significantly shorter distant metastasis-free survival (HR, 9.0; 95% CI, 2.6-31.7; P < .0001; FIGURE). The risk score was superior to tumor and nodal stage for distant metastatic prognostication and remained significant after multivariate adjustment. The genetic score had improved predictive value for distant treatment failure in an elevated risk subgroup of cancers negative for human papillomavirus, an increasingly prevalent cause of head and neck cancer among nonsmokers (HR, 20.8; 95% CI, 2.6-166; P = .004).

Gene expression from cancer samples are calculated as an average of admixed cellular genetics profiles of not only cancer cells, but also immune cells and supportive tissues. To get a better grasp of what is actually occurring within the tumor microenvironment, investigators applied single-cell RNA sequencing to approximate the distribution of various cell type proportions. Single-cell deconvolution study results revealed a significant increase in cancer-associated fibroblasts and T-cell subpopulation dysregulation within the tumor microenvironment among patients with distant metastatic treatment failure.

Current paradigms of cancer treatment are centered around targeting tumor cells. These treatments are often not enough to completely eradicate cancer, as the supportive cancer stroma may enable tumor recurrence and therapeutic resistance. In the past few years, available cancer therapies have expanded to improve...
endogenous immune cell responses through checkpoint blockades. We have seen a distinct benefit observed in some patients, including those with recurrent head and neck setting. However, efforts to replicate these successes for the definitive management of nonmetastatic advanced head and neck cancers have been unsuccessful. One hypothesis is that T cells enable resistance to checkpoint inhibition in the microenvironment through cancer-associated fibroblast–TGF-β signaling. The microenvironment within head and neck cancers commonly consists of more than 80% fibroblasts. These fibroblasts are critical for various functions that regulate cancer progression through secreting soluble factors, metabolic effects, remodeling the extracellular matrix, and immune crosstalk. Furthermore, the stromal and immune cell composition of head and neck cancers have been demonstrated to be independent predictors of nodal metastasis and epithelial-mesenchymal transformation in results of single-cell, comparative, and cell culture studies. Thus, targeting this unique cell population within the tumor microenvironment of locally advanced head and neck cancer represents a promising, yet underexplored, method for overcoming treatment resistance.

The predictive risk-score research serves as the basis for the development of preclinical models to evaluate the feasibility of adjuvant tumor microenvironment modification with the goal of reducing the rate of distant metastatic disease.

REFERENCE

Mo et al’s research, awarded first place in a paper session at the 2020 annual New York Head & Neck Society meeting, was presented during an oral scientific session at the 2020 American Society for Radiation Oncology Annual Meeting.
Multimodal Approaches May Improve Outcomes in Advanced Cancer of the Cervix

by MAURIE MARKMAN, MD

THE MANAGEMENT OF CARCINOMA OF THE CERVIX

of the cervix represents a remarkable dichotomy. On the one hand, we have the well-established, truly major public health success associated with population-based screening for the malignancy; more recent, increasingly solid evidence for the actual prevention of the disease as a result of effectively implemented human papillomavirus (HPV) vaccination strategies; and, finally, the documented survival benefits associated with the delivery of a multimodality radiation plus systemic chemotherapy, or chemoradiation, approach in the management of locally advanced disease. However, on the other hand, one must now consider the unquestionably objective marginal effectiveness of current therapeutics directed to favorably influence the natural history of recurrent or metastatic cancers.

Today, the medical community possesses diagnostic tools that can detect, with great sensitivity and specificity, early-stage invasive disease. Additionally, these diagnostics can detect abnormalities such as high-grade dysplasia and carcinoma in situ of cervical cancer that, in the majority of cases, can be effectively managed with the elimination of the potential for tumor progression. Further, vaccination against the HPV types known to be etiologic in causing 70% to 90% of all cervical cancers has the potential to rather dramatically reduce the risks of the development of a cancer responsible for 600,000 new cases and over 300,000 deaths worldwide each year.

Yet, when cervix cancer is detected with documented metastatic disease or the malignancy recurs following definitive local therapy with either surgery or radiotherapy, currently available systemic antineoplastic strategies, unfortunately, remain distressingly limited in their clinical utility.

SYSTEMIC CYTOTOXIC CHEMOTHERAPY

Cisplatin has been the cornerstone of the chemotherapeutic management of carcinoma of the cervix for more than 4 decades. Over this extended time interval, randomized trials have explored various doses and schedules for delivery of this agent in the management of metastatic or recurrent disease. The chemotherapy regimen of cisplatin and external beam radiation in these difficult clinical settings has also been approved by the FDA for use in the management of cervical cancer with no evidence for the superiority of a more intensive program in the management of metastatic or recurrent disease.

Carboplatin has also been examined for its utility in this clinical setting and, although clearly active, is somewhat less preferred compared with cisplatin due to the frequent prior use of pelvic radiation in disease management. Under these circumstances, carboplatin, being more marrow suppressive than cisplatin, is associated with a greater risk of producing serous bone marrow suppression and subsequent infection.

Cisplatin-based combination chemotherapy regimens have been extensively explored over the past several decades in the management of metastatic and recurrent disease. Today, the most widely employed combination regimen is likely cisplatin plus paclitaxel, although cisplatin plus topotecan has also been approved by the FDA for use in this clinical setting.

One clinically relevant difficulty associated with determining optimal chemotherapy in the management of cervical cancer is the established role played by cisplatin-based chemoradiation in the multimodality management of high-risk and locally advanced disease. Several landmark phase 3 randomized trials confirmed the overall survival benefits associated with the concurrent administration of cisplatin and external beam radiation in these difficult clinical settings.

As a result, for a patient who subsequently experiences evidence of persistent or recurrent disease following the delivery of cisplatin as a radiosensitizer (eg, 50 mg/m^2 per week during external beam radiation), the continued utility of platinum-based chemotherapy remains quite uncertain.

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be effectively utilized where a patient has previously received cisplatin as a component of a chemoradiation strategy, the National Cancer Institute–affiliated Gynecologic Oncology Group (GOG) directly compared the combination of cisplatin plus paclitaxel to a non–platinum-containing regimen of paclitaxel plus topotecan in metastatic or recurrent carcinoma of the cervix. Unfortunately, the results failed to reveal any evidence for the superiority of the non-platinum-containing regimen despite the prior delivery of platinum to this patient population. Further, the 2-drug combination of paclitaxel and topotecan might represent the 2 most “active” non-platinum cytotoxic agents in the malignancy. No other experience is required to emphasize the magnitude of the limited utility of cytotoxic drugs in cervical cancer.

Although other single agents in this class may be used to provide some degree of palliative relief for individual patients with cervical cancer, the overall efficacy of such a strategy is marginal, with ORRs anticipated to be less than 10%. In addition, tumor regressions in this setting are generally of short duration.

It should also be noted that the likelihood of a clinical response being observed in the setting of recurrent or metastatic cervix cancer will be reduced in body regions (eg, pelvis) previously exposed to external beam radiation, likely due to limited blood supply and the presence of a resistant cancer cell population. GOG investigators observed several clinical features that predicted a reduced likelihood of response in an analysis of their experience with platinum-based chemotherapy in addition to previous pelvic radiation. These features included performance status higher than 0, prior treatment with a chemosenstization regimen, time interval from diagnosis to first recurrence of less than 1 year, presence of pelvic disease, and being African American.

### ROLE OF BEVACIZUMAB IN SYSTEMIC MANAGEMENT

GOG investigators subsequently examined the efficacy of the antiangiogenic agent, bevacizumab (Avastin), in a group of patients with persistent and recurrent cervical cancer and observed an ORR of 11% (n = 46 patients) with a median duration of response of 6.2 months. The toxicity profile of the agent was similar to that observed and anticipated in a relatively heavily pretreated patient population.

These data led to the initiation of a somewhat complex randomized GOG-0240 trial (NCT00803062) with a 2 × 2 factorial design examining the addition of bevacizumab to a regimen of cisplatin plus paclitaxel or paclitaxel plus topotecan in patients with recurrent, persistent, or metastatic cervical cancer. The addition of bevacizumab led to a statistically significant improvement in median overall survival (17.0 vs 13.3 months, respectively; HR, 0.71; P = .004). The FDA has approved bevacizumab for the treatment of metastatic cervical cancer; however, the addition of the agent to cytotoxic chemotherapy is restricted to a patient population with a reasonably good performance status (TABLE). Further, the adverse effects of bevacizumab, particularly wound healing and the potential for vascular complications, need to be carefully considered for patients undergoing surgery of curative or palliative intent as a component of a multidisciplinary treatment plan.

### IMMUNOTHERAPEUTIC APPROACHES

The current focus in innovative strategies for the management of advanced cervical cancer is in the domain of immunotherapy. Similar to clinical situations across cancer types, several checkpoint inhibitors have been examined in patients who have recurrent or persistent disease after primary treatment, including cisplatin-based therapies. Evidence of therapeutic benefit, including objective responses (approximately 10%-20%) often of unexpected prolonged duration (> 6 months), has been confirmed.

In addition, a number of novel strategies, including combination checkpoint inhibitors, tumor vaccines, and adoptive T-cell therapies, are under active investigation in the management of recurrent and persistent cervical cancer. Investigators anticipate that over the next several years, 1 or more of these approaches will be demonstrated to favorably affect the natural history of this difficult malignancy.

---

**TABLE. Approval Snapshot: Bevacizumab (Avastin)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bevacizumab plus chemotherapy (N=227)</th>
<th>Chemotherapy alone (N=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>16.8 (HR, 0.74; 95% CI, 0.58-0.94; P=.0132)</td>
<td>12.9</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>45% (39%-52%)</td>
<td>34% (28%-40%)</td>
</tr>
</tbody>
</table>

**Adverse events**

The most common adverse events (≥ 20%) are fatigue, decreased appetite, hyperglycemia, hypomagnesemia, weight loss, hypertension, urinary tract infection, and headache.

ORR, objective response rate; OS, overall survival.
Charting the Course for Patients With High-Risk Colon Cancer: 3 Months Versus 6 Months

by Alexandre A. Jácome, MD, PhD; and Cathy Eng, MD

COLORECTAL CANCER (CRC) IS the second most common cause of cancer-related death in the United States.1 Despite recent improvements in screening rates, most patients with colon cancer (CC) receive a diagnosis of locally advanced disease (T3/T4 and/or node-positive) at first presentation.1 In 5 years, it is estimated that approximately 20% of patients with stage II disease and 35% with stage III disease will experience disease recurrence.2,4 These estimates highlight the need to pursue progress in adjuvant systemic therapy in order to decrease recurrence rates and improve survival.

Fluoropyrimidine-based adjuvant chemotherapy has been the standard of care of stage III CC for the past 30 years.2,4 However, the routine use of adjuvant chemotherapy in stage II CC has not been recommended, since the small improvements in disease-free survival (DFS) and in overall survival (OS) do not outweigh the expected rate of acute and late fluorouracil (5-FU)-related adverse events (AEs).5 Nevertheless, patients with stage II CC include a heterogeneous group who present with different risks of recurrence. The selection of patients with stage II disease who presumably derive larger benefit from adjuvant chemotherapy is based on the presence of T4 or high-risk clinicopathologic factors, which offer an inaccurate risk stratification in low- and high-risk stage II CC. There is no consensus regarding the clinicopathologic factors that should be considered in risk stratification. The National Comprehensive Cancer Network (NCCN) guidelines do not consider the use of adjuvant 5-FU in patients with stage II CC who have fewer than 12 lymph nodes analyzed in the surgical specimen; poorly differentiated histology; lymphatic/vascular invasion; bowel obstruction; peritoneal invasion; localized perforation; and close, indeterminate, or positive margins.6 Likewise, the European Society for Medical Oncology guidelines take into account the presence of T4 or high preoperative carcinoembryonic antigen levels, in addition to the NCCN criteria.7

The only predictive biomarker used in the selection of this patient population is the high-frequency microsatellite instability (MSI-H) status, expected to be found in approximately 15% of the stage II population. Patients with MSI-H tumors present a lower risk of recurrence and do not derive benefit from adjuvant chemotherapy with 5-FU alone, even if they are classified as high risk based on the aforementioned clinicopathologic factors.5,9 The identification of prognostic and predictive factors for a more accurate selection of patients with stage II CC who will benefit from adjuvant chemotherapy is urgently needed.

STAGE III: OXALIPLATIN-BASED ADJUVANT CHEMOTHERAPY FOR 3 MONTHS OR 6 MONTHS?

Data from MOSAIC (NCT00275210) have established folinic acid (leucovorin), 5-FU, and oxaliplatin (FOLFOX) as the standard adjuvant therapy for stage III CC.10 Six-year follow-up data demonstrated that 6 months of FOLFOX was associated with a 7.5% absolute reduction in the risk of recurrence and 4.2% reduction in the risk of death in patients with stage III disease.4 Further studies confirmed the benefit of oxaliplatin-based adjuvant chemotherapy, including if used with either capecitabine (CAPOX) or bolus 5-FU (FLOX), with similar efficacy but with different toxicity profiles compared with infusional 5-FU.11,12 Therefore, apart from elderly patients, who might be considered to receive fluoropyrimidine alone because they derive a lower benefit from the addition of oxaliplatin,5 6-month oxaliplatin-based adjuvant chemotherapy should be offered to all patients with node-positive disease, irrespective of their T stage.

Nevertheless, 6-month oxaliplatin may be associated with several cumulative AEs, such as fatigue; liver injury; hypersplenism; and, mainly, peripheral neuropathy.14 Despite presenting a gradual resolution, approximately 15% of patients will experience grade 1 or higher neurotoxicity for over 4 years.4 To decrease the burdensome effects of oxaliplatin with a minimal loss of survival benefit, a noninferiority study (IDEA collaboration) was designed with the goal of prospectively pooling data from 6 randomized clinical trials of adjuvant therapy in patients with stage III CC to evaluate the hypothesis that 3 months of oxaliplatin-based therapy (FOLFOX or CAPOX) would be noninferior to 6 months in 3-year DFS.15

CONTINUED ON PAGE 68

“ The incorporation of prognostic and predictive biomarkers, such as Immunoscore and ctDNA, has the potential to bring precision medicine to the adjuvant therapy of colon cancer.”
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IDEA collaboration was composed of 6 phase 3 clinical trials: CALGB/SWOG 80702, IDEA France, SCOT, ACHIEVE, TOSCA, and HORG (TABLE 1). In total, they evaluated 12,834 patients, of which approximately 60% were treated with FOLFOX and 40% with CAPOX. At a median follow-up of 41.8 months, noninferiority of 3 months of therapy versus 6 months was not confirmed in the modified intention-to-treat population. The 3-year DFS, the primary end point, in the 3-month group was 74.6% versus 75.3% in the 6-month group (HR, 1.07; 95% CI, 1.00-1.15; \( P = .11 \) for noninferiority of 3-month therapy; \( P = .045 \) for superiority of 6-month therapy). Noninferiority of 3 months versus 6 months could be claimed if the upper limit of the 2-sided 95% CI of the HR did not exceed 1.12.

Updated data presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program showed a 5-year OS of 82.4% versus 82.8%, respectively (HR, 1.02; 95% CI, 0.95-1.11; \( P = .0583 > 0.025 \) to reject the null hypothesis). On the other hand, the shorter duration of adjuvant therapy was noninferior to the longer duration among the patients who received FOLFOX (HR, 0.98; 95% CI, 0.88-1.08). The interaction test was significant in the updated analysis (\( P = .0113 \)).

Subgroup analysis based on T and N stage also revealed a differential benefit of treatment duration. In patients deemed low risk with T1-3, N1 disease, 3-month therapy was noninferior to 6-month in 3-year DFS (HR, 1.01; 95% CI, 0.90-1.12). However, among the patients with high-risk cancers, T4 or N2, 6 months of therapy was superior to 3 months (HR, 1.12; 95% CI, 1.03-1.23; \( P = .01 \) for superiority). The interaction test between therapy duration and risk group was not significant (\( P = .11 \))

In the 8th edition of AJCC: Cancer Staging Manual, patients with no regional lymph node metastases but with tumor deposits are staged as pN1c. However, the number of tumor deposits is not considered in the TNM staging system. The post hoc analysis of IDEA France suggests that pN1 patients who are restaged as pN2 based on the number of tumor deposits should be managed as high-risk stage III patients.

Interestingly, a differential efficacy according to chemotherapy regimen was observed. Among the patients treated with FOLFOX, 6-month therapy was superior to 3-month in 3-year DFS (HR, 1.16; 95% CI, 1.07-1.26; \( P = .001 \) for superiority of 6-month therapy). On the other hand, the shorter duration of adjuvant therapy was noninferior to the longer duration among the patients with high-risk cancers, T4 or N2, 6 months of therapy was superior to 3 months (HR, 1.12; 95% CI, 1.03-1.23; \( P = .01 \) for superiority). The interaction test between therapy duration and risk group was not significant (\( P = .11 \)). Further, 3 months of CAPOX compared well with 6 months even among the high-risk group (HR, 1.02; 95% CI, 0.89-1.17). But, independent of risk group, outcomes after 3 months of FOLFOX therapy were worse than those after 6 months.

The recently published post hoc analysis of the phase 3 IDEA France study (NCT00958737) showed the prognostic impact of tumor deposits in the DFS of patients with stage III CC. Tumor deposits were detected in 9.5% of patients (n = 181), who also presented with worse 3-year DFS: 65.6% versus 74.7% in patients with no tumor deposits (\( P = .007 \)). Even in multi-variable analysis adjusted for duration of adjuvant therapy, tumor deposits remained a strong prognostic factor (HR, 1.4; 95% CI, 1.1-1.8; \( P = .020 \)). Interestingly, when the number of tumor deposits was added to the number of positive lymph nodes, 2.4% of the patients initially staged as pN1 were restaged as pN2. These restaged patients presented lower 3-year DFS compared with the pN1 population (60.7% vs 79.3%, respectively; \( P = .015 \)), with similar 3-year DFS to those patients initially staged as pN2. This study sheds light on the potential influence of the number of tumor deposits on the decision about the duration of adjuvant therapy (FIGURE 1).

In the 8th edition of AJCC: Cancer Staging Manual, patients with no regional lymph node metastases but with tumor deposits are staged as pN1c. However, the number of tumor deposits is not considered in the TNM staging system. The post hoc analysis of IDEA France suggests that pN1 patients who are restaged as pN2 based on the number of tumor deposits should be managed as high-risk stage III patients.

### TABLE 1. IDEA Collaboration Trials With Respective Characteristics and Efficacy Results

<table>
<thead>
<tr>
<th>Trial (ClinicalTrials.gov identifier)</th>
<th>N</th>
<th>Stage</th>
<th>Regimen</th>
<th>3-year DFS (3 months vs 6 months)</th>
<th>5-year OS (3 months vs 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80702 (NCT01150045)</td>
<td>2526</td>
<td>III</td>
<td>FOLFOX</td>
<td>71.9% vs 75.0% (HR, 1.14; 95% CI, 0.92-1.14)</td>
<td>82.8% vs 80.8% (HR, 0.86; 95% CI, 0.66-1.12)</td>
</tr>
<tr>
<td>IDEA France (NCT00958737)</td>
<td>2010</td>
<td>III</td>
<td>FOLFOX (90%) CAPOX (10%)</td>
<td>72.0% vs 76.0% (HR, 1.24; 95% CI, 1.05-1.46)</td>
<td>NR</td>
</tr>
<tr>
<td>SCOT (NCT00749450)</td>
<td>6088</td>
<td>High-risk II (18%) III (88%)</td>
<td>FOLFOX (33%) CAPOX (67%)</td>
<td>76.7% vs 77.1% (HR, 1.00; 95% CI, 0.90-1.11)</td>
<td>90.0% vs 89.6%* (HR, 0.99; 95% CI, 0.96-1.14)</td>
</tr>
<tr>
<td>ACHIEVE-2*</td>
<td>1313</td>
<td>III</td>
<td>FOLFOX (25%) CAPOX (75%)</td>
<td>79.5% vs 77.9% (HR, 0.95; 95% CI, 0.76-1.20)</td>
<td>NR</td>
</tr>
<tr>
<td>TOSCA (NCT00646607)</td>
<td>3759</td>
<td>High-risk II (35%) III (65%)</td>
<td>FOLFOX (64%) CAPOX (36%)</td>
<td>81.1% vs 83.0% (HR, 1.14; 95% CI, 0.99-1.32)</td>
<td>NR</td>
</tr>
<tr>
<td>HORG (NCT01308086)</td>
<td>1115</td>
<td>High-risk II (37%) III (63%)</td>
<td>FOLFOX (35%) CAPOX (65%)</td>
<td>77.2% vs 77.9% (HR, 1.05; 95% CI, 0.61-1.55)</td>
<td>NR</td>
</tr>
</tbody>
</table>

FOLFOX, folinic acid (leucovorin), fluorouracil, and oxaliplatin; NR, not reported; OS, overall survival.

*Three-year OS.

*Study conducted in Japan.
HIGH-RISK STAGE II: 5-FU ALONE OR OXALIPLATIN-BASED ADJUVANT CHEMOTHERAPY?

The routine use of any modality of adjuvant chemotherapy in patients with stage II CC has not been recommended. However, some of these patients present a similar or even higher risk of recurrence compared with stage III CC. Investigators enrolled 899 patients with stage II CC to the MOSAIC trial, and these patients did not derive statistically significant benefit from the addition of oxaliplatin, both in DFS and OS, even in the exploratory analysis of the high-risk population, defined as patients who presented at least 1 of the following: T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion, or fewer than 10 lymph nodes examined.\(^1\)

Additionally, 4 of the 6 clinical trials that composed IDEA collaboration included patients with stage II CC (TABLE 2).\(^{18,20,21,24}\) In total, 3273 patients with high-risk stage II CC were enrolled, despite having no consensus on the definition criteria of high-risk disease, which varied slightly among the 4 studies.

FOLFOX and CAPOX regimens were used in 1254 and 2019 patients, respectively. In a pooled analysis of the 4 trials, noninferiority of 3 months of therapy could not be demonstrated. The 5-year DFS rate was 80.7% with the 3-month regimen versus 84.0% with the 6-month regimen (HR, 1.18; 80% CI, 1.05-1.31; \(P = .67\)). Based on the data from the pooled analysis, these patients should be treated with 6-month oxaliplatin-based adjuvant therapy. Nevertheless, it has never been demonstrated that oxaliplatin plus fluoropyrimidine is superior over fluoropyrimidine alone in this population. None of the included trials had a third comparator arm for fluoropyrimidine alone.

So, should a subgroup of stage II high-risk patients be treated with oxaliplatin-based adjuvant therapy? In the overall population of the IDEA collaboration, noninferiority of 3-month therapy could not be demonstrated in T4 patients (HR, 1.16; 95% CI, 1.03-1.31).\(^{15}\) Similarly, in a multivariable analysis of the Japanese ACHIEVE-2 trial, disease classified as T4 and involving fewer than 12 lymph nodes remained independent significant negative prognostic factors. Therefore, it is plausible to consider 3 months of oxaliplatin-based adjuvant therapy in patients who are staged T4, N0 or those with fewer than 12 lymph nodes harvested (FIGURE 2). Based on the overall findings from IDEA, it would be counterintuitive to offer 6 months of oxaliplatin-based adjuvant therapy in patients who are N0.

**FIGURE 1.** Duration of Adjuvant Therapy in Stage III Colon Cancer

![Duration of Adjuvant Therapy in Stage III Colon Cancer](image)

**TABLE 2.** Efficacy Results of High-Risk Stage II Patients in IDEA Collaboration Trials\(^{18,20,21,24}\)

<table>
<thead>
<tr>
<th>Trial (ClinicalTrials.gov identifier)</th>
<th>N</th>
<th>3-year DFS (3 months vs 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCOT (NCT00749450)*</td>
<td>1096</td>
<td>HR, 0.98; 95% CI, 0.74-1.31</td>
</tr>
<tr>
<td>TOSCA (NCT00646607)*</td>
<td>1253</td>
<td>Unadjusted HR, 1.41; 95% CI, 1.05-1.89; (P = .022)</td>
</tr>
<tr>
<td>HORG (NCT01308086)*</td>
<td>413</td>
<td>HR, 1.05; 95% CI, 0.68-1.63; (P = .829)</td>
</tr>
<tr>
<td>ACHIEVE-2*</td>
<td>525</td>
<td>HR, 1.12; 95% CI, 0.67-1.87; (P = .67)</td>
</tr>
</tbody>
</table>

DFS, disease-free survival.

*SCOT high-risk stage II population defined as meeting 1 or more of the following criteria: T4 disease, tumor obstruction with or without perforation of the primary tumor preoperatively, fewer than 10 lymph nodes harvested, poorly differentiated histology, perineural invasion, or extramural venous or lymphatic vascular invasion.

*TOSCA high-risk stage II population defined as meeting 1 or more of the following criteria: T4 tumor, adequate histology, less than 12 lymph nodes harvested, poorly differentiated histology, perineural invasion, or extramural venous or lymphatic vascular invasion.

*HORG high-risk stage II population defined as meeting 1 or more of the following criteria: T4 tumor, grade greater than 3, vessels/neural invasion, obstruction/perforation, and fewer than 12 nodes retrieved.

*ACHIEVE-2 high-risk stage II population defined as meeting 1 or more of the following criteria: T4 tumor, inadequate nodal harvest less than 12, poorly differentiated, clinical sign of obstruction, and perforation or vascular invasion.

**PERSPECTIVES**

The decision to offer adjuvant therapy and its duration is regularly based on the TNM classification system, which provides useful yet incomplete prognostic information. Tumor infiltration by immune cells has been demonstrated to be valuable prognostic information. CD3+ and CD8+ T cells in the tumor microenvironment may be measured and stratified by an Immunoscore, which separates the tumors into 3 categories: low (0%-25%), intermediate (25%-70%), and high (70%-100%).\(^{26}\)

In data from a cohort of 1434 patients with stage II CC, Immunoscore was the highest relative contribution to the risk of recurrence of all clinical parameters, including the TNM classification system.\(^{26}\) Likewise, in a cohort of 763 patients with stage III CC, those with a high Immunoscore presented with the...
lowest risk of recurrence: 3-year recurrence-free rates were 56.9%, 65.9%, and 76.4% in patients with low, intermediate, and high Immunoscore, respectively (HR for high vs low, 0.48; 95% CI, 0.32-0.71; \( P = .0003 \)).

In multivariable analysis, Immunoscore was an independent prognostic variable for time to recurrence, even when adjusted for T stage, N stage, sidedness, and MSI status. Interestingly, adjuvant chemotherapy was significantly associated with survival in the high-Immunoscore group for patients with both low-risk and high-risk stage III disease but not in the low-Immunoscore group.

Promising strategies to detect postoperative minimal residual disease through identification of circulating tumor DNA (ctDNA) have been described in CRC. In a cohort of 130 patients with stage I to III CRC, those who were ctDNA positive at postoperative day 30 were 7 times more likely to relapse than those who were ctDNA negative (HR, 7.2; 95% CI, 2.7-19.0; \( P < .001 \)).

Notably, those who were ctDNA positive following completion of adjuvant chemotherapy were 17 times more likely to relapse (HR, 17.5; 95% CI, 5.4-56.5; \( P < .001 \)). In multivariate analyses, ctDNA status was independently associated with relapse after adjusting for known clinicopathologic risk factors. In addition, serial ctDNA analyses revealed disease recurrence up to 16.5 months ahead of standard radiologic imaging. COBRA (NCT04068103), a randomized phase 2/3 study, is under way to evaluate ctDNA as a predictive biomarker in adjuvant chemotherapy of patients with stage IIA CC.

Given the demonstrated benefit of immunotherapy in MSI-H metastatic CRC, an ongoing phase 3 study (NCT02912559) is evaluating the benefit of atezolizumab (Tecentriq) plus chemotherapy compared with chemotherapy alone in patients with stage III CC and MSI-H tumors. Furthermore, the optimistic results of genome-guided personalized therapy in metastatic disease, such as targeted therapy for patients who harbor BRAF V600E mutation, HER2 amplification, and NTRK fusion, provide hope that investigators will be able to address the potential benefit of targeted therapy in localized disease.

CONCLUSIONS
Most patients with stage II and III CC are cured by surgery only. The identification of a subgroup of patients who need adjuvant chemotherapy thus far has been inaccurate. The decision to offer adjuvant chemotherapy based on the classical clinicopathologic factors induces a high risk of both overtreatment and undertreatment. The incorporation of prognostic and predictive biomarkers, such as Immunoscore and ctDNA, has the potential to bring precision medicine to the adjuvant therapy of CC.

The IDEA collaboration has brought vital elements to the shared decision-making process among patients and oncologists, who should consider the benefits of each regimen, its duration, and the treatment-related AEs, as well as the patient’s preferences, age, comorbidities, and expectations in the choice of adjuvant therapy.

In summary, it is acceptable to offer 3 months of CAPOX for patients with stage T1-3, N1 CC. Patients with T4 or N2 disease should be considered for 6-month oxaliplatin-based therapy, or 3 months of CAPOX if a minimal loss of benefit in DFS and OS is agreeable. Tumor deposits have demonstrated use as a robust prognostic factor, and their influence in determining the duration of adjuvant therapy should be carefully examined in further studies.

Although randomized clinical trials designed to specifically address the benefit of oxaliplatin in the adjuvant therapy of high-risk stage II CC have not finished, the standard of care remains fluoropyrimidine alone. Patients with stage II CC who have fewer than 12 lymph nodes examined or with T4, N0 disease may be considered for 3 months of CAPOX.

For a full list of references, see the article at https://bit.ly/3hVGy5e.

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WHEN HER2+ MBC PROGRESSES

PURSUE UNPRECEDENTED SURVIVAL

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine

Reduced risk of disease progression or death by 46%

Median PFS: 7.8 months (95% CI: 7.5–9.6) vs 5.6 months (95% CI: 4.2–7.1); HR = 0.54 (95% CI: 0.42–0.71); P <0.00001

Extended median OS by 4.5 months

Median OS: 21.9 months (95% CI: 18.3–31.0) vs 17.4 months (95% CI: 13.6–19.9); HR = 0.66 (95% CI: 0.50–0.87); P = 0.0048

The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.

Tukatinib(TUKYSA)+ trastuzumab + capecitabine is the only Category 1 recommended regimen for second-line systemic treatment of HER2+ MBC by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer*

Indication

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Safety Information

Warnings and Precautions

- Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Cl = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.

*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.

†Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Please see full Important Safety Information on the following pages.
RAISING THE STANDARD FOR SURVIVAL

In combination with trastuzumab + capecitabine

**TUKYSA extended overall survival**

**4.5 MONTH IMPROVEMENT IN MEDIAN OS**

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

**Important Safety Information**

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required in HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo–Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock. Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-planter erythrodysesthesis, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.
In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

**PRIMARY ENDPOINT**

**PFS**

46% reduction in the risk of disease progression or death

- HR = 0.54 (95% CI: 0.42-0.71); P < 0.00001
- Median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.6 months (95% CI: 4.2-7.1) in the control arm

**EXPLORATORY ANALYSIS**

**PFS IN PATIENTS WITHOUT BRAIN METASTASES**

43% reduction in the risk of disease progression or death

- HR = 0.57 (95% CI: 0.41-0.80)
- Median PFS: 9.6 months (95% CI: 7.6-12.4) in the TUKYSA arm (n=211) vs 6.8 months (95% CI: 4.3-9.3) in the control arm (n=108)

*Study design: HER2CLIMB was a randomized (2:1), double-blind, placebo-controlled trial of 812 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm; n = 410) or placebo + trastuzumab + capecitabine (control arm; n = 212). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause). PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.  

*This exploratory analysis was not controlled for a type 1 error, and HER2CLIMB was not powered to test this endpoint. Results are descriptive only and not contained in the approved product labeling.

BICR = blind independent central review; CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; PPE = palmar-plantar erythrodysesthesia; RECIST = Response Evaluation Criteria in Solid Tumors.

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST. The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**

- **Strong CYP3A/Moderate CYP2C8 Inducers**: Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.

- **Strong or Moderate CYP2C8 Inhibitors**: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity: avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

- **CYP3A Substrates**: Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

- **P-gp Substrates**: Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**

- **Lactation**: Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.

- **Renal Impairment**: Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (ClCr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.

- **Hepatic Impairment**: Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References:
2. Reference with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (v3.2020). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed July 29, 2020. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for the application or use in any way.
TUKYSA® (tucatinib) tablets, for oral use

INDICATIONS AND USAGE
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced, unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSEAGE AND ADMINISTRATION
Recommended Dosage
The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity. Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time.

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions
The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>Grade (%)</td>
<td>Grade (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other adverse reactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS
Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN. 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternally exposures ≥1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information for trastuzumab and capecitabine for pregnancy and contraception information.

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

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors: Avoid concomitant use of strong CYP2C8 inhibitors. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Severe Hepatic Impairment: For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

CONTRAINDICATIONS
None.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA (N=404)</th>
<th>Placebo (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>Grade (%)</td>
<td>Grade (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>61 12 0.5 53 9 0</td>
<td>58 3.7 0 44 3 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>68 0.7 0 25 3.6 0</td>
<td>68 3.7 0 44 3 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 0 0 25 3.6 0</td>
<td>26 0 0 25 3.6 0</td>
</tr>
<tr>
<td>Rash</td>
<td>20 0.7 0 15 0.5 0</td>
<td>20 0.7 0 15 0.5 0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity³</td>
<td>42 9 0.2 24 3.6 0</td>
<td>42 9 0.2 24 3.6 0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 0.5 0 20 0 0</td>
<td>25 0.5 0 20 0 0</td>
</tr>
</tbody>
</table>
with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

**Lactation**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfeeding child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

**Females and Males of Reproductive Potential**

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

**Pediatric Use:**

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

**Geriatric Use:**

In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

**Renal Impairment:**

The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (Clcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [Clcr] 30 to 89 mL/min).

**Hepatic Impairment:**

Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

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**Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine</th>
<th>Placebo + Trastuzumab + Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥3</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>59</td>
<td>33</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>47</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>Increased AST</td>
<td>43</td>
<td>6</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>40</td>
<td>0.8</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>28</td>
<td>2.5</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCl CTCAE v5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v4.03.
5. Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increased persistently throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**DRUG INTERACTIONS**

**Effects of Other Drugs on TUKYSA**

**Strong CYP3A Inducers or Moderate CYP2C8 Inducers:** Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

**Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor.

**Effects of TUKYSA on Other Drugs**

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates.
RET Joins the Ranks of Actionable Targets in Precision Oncology

by JANE DE LARTIGUE, PhD

OVER THE PAST 2 DECADES, a growing number of targetable tumor-specific molecular alterations have been identified, ushering in the era of precision oncology.¹ Now, alterations in the RET gene can be added to the list of druggable targets.²³

RET is not a new target; it was first linked to cancer more than 30 years ago. RET-directed therapeutics have included multikinase inhibitors with RET among their targets.²³ Although several are approved for the treatment of thyroid cancers, which frequently display RET alterations, RET biomarker testing is not required.⁴⁻⁷

In less than a year, the FDA has approved 2 selective RET inhibitors, selpercatinib (Retevmo) and pralsetinib (Gavreto) for the treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring a RET fusion and for RET-altered thyroid cancers.⁸⁻¹⁰

Selective RET inhibitors have demonstrated potent and durable efficacy in patients with RET-altered tumors, including those with RET mutations that confer resistance to multikinase inhibitors.¹¹⁻¹⁴ Building on past experience with targeted therapies, investigators have begun to anticipate novel mechanisms of resistance to these agents.²⁻¹⁵

TPX-0046, a next-generation inhibitor of both RET and a second kinase, SRC, has demonstrated preclinical efficacy against one such mechanism of resistance, RET solvent front mutations, and is already in clinical development.¹⁶

RET alterations occur infrequently outside of thyroid cancer. However, the advent of next-generation sequencing (NGS) technologies has revealed their presence in a growing number of tumor types, suggesting a tumor-agnostic role for RET inhibitors in the future.²⁻¹⁷ The clinical development of selective and multitargeted RET inhibitors is underway for approved and novel agents, according to ClinicalTrials.gov (TABLE).

TABLE. Ongoing Clinical Trials Targeting RET Alterations

<table>
<thead>
<tr>
<th>Drug/developer</th>
<th>Trial description (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective RET inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Selpercatinib</td>
<td>Phase 3</td>
</tr>
<tr>
<td>(Retevmo) Eli Lilly and Company</td>
<td>— Versus physician’s choice of cabozantinib or vandetanib in kinase inhibitor-naïve, RET-mutant MTC (LIBRETTO-531/NCT04211337)</td>
</tr>
<tr>
<td></td>
<td>— Versus permetrex platinum doublet chemotherapy +/- pembrolizumab in frontline treatment of advanced RET fusion-positive NSCLC (LIBRETTO-431/NCT04194944)</td>
</tr>
<tr>
<td></td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>— With oemertinib in RET fusion-positive NSCLC that progressed on frontline oemertinib (ORCHARD/NCT03944772)</td>
</tr>
<tr>
<td></td>
<td>— RET-altered advanced solid tumors (LIBRETTO-321/NCT04280081)</td>
</tr>
<tr>
<td></td>
<td>— RET-altered advanced solid tumors or lymphomas (NCT04320888; NCT03155620)</td>
</tr>
<tr>
<td></td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>— RET-altered advanced solid tumors (LIBRETTO-001/NCT03157128)</td>
</tr>
<tr>
<td>Pralsetinib</td>
<td>Phase 3</td>
</tr>
<tr>
<td>(Gavreto Blueprint Medicines)</td>
<td>— Versus platinum doublet chemotherapy +/- pembrolizumab in frontline treatment of RET fusion-positive metastatic NSCLC (AcceleRET Lung/NCT04222972)</td>
</tr>
<tr>
<td></td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>— RET-altered advanced solid tumors (ARROW/NCT03037385)</td>
</tr>
<tr>
<td>BOS172738</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Boston Pharmaceuticals</td>
<td>— RET-altered advanced solid tumors (NCT03780517)</td>
</tr>
<tr>
<td><strong>Dual RET/SRC inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>TPX-0046 Turning Point Therapeutics</td>
<td>Phase 1/2 — RET-altered advanced solid tumors (NCT04161391)</td>
</tr>
<tr>
<td><strong>Multikinase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Phase 2</td>
</tr>
<tr>
<td>(Cabometyx Exelixis)</td>
<td>— RET fusion-positive advanced NSCLC (CRETA/NCT04131543; NCT01639508)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Phase 2</td>
</tr>
<tr>
<td>(Iclusig Takeda Pharma Company Limited)</td>
<td>— RET-mutant advanced MTC (NCT03838692)</td>
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<tr>
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<td>— RET-altered advanced solid tumors (NCT02272998)</td>
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<tr>
<td>Alectinib</td>
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</tr>
<tr>
<td>(Alecensa Genentech)</td>
<td>— Previously treated RET fusion-positive NSCLC ( ALERT-lung/NCT03445000)</td>
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<tr>
<td>Sunitinib</td>
<td>Pilot study</td>
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<tr>
<td>(Sutent Pfizer)</td>
<td>— RET fusion-positive refractory solid tumors (NCT02450123)</td>
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MTC, medullary thyroid cancer; NSCLC, non–small cell lung cancer.

RET KINASE SIGNALING

Under normal conditions, RET signaling plays a vital role in a number of cellular processes, including development of the central and peripheral nervous systems as well as the kidney.²⁻¹⁸

Aberrant RET activity has been linked to cancer development since the 1980s. Its name, which stands for REarranged during Transfection, reflects its oncogenic role; RET was first discovered as a gene that was rearranged following transfection of mouse embryonic fibroblasts with human lymphoma DNA.²⁻¹⁸

The RET tyrosine kinase receptor transmits its signals by interacting with the glial cell line derived neurotrophic factor (GDNF) family of ligands, including GDNF, neurturin, artemin, and persephin (FIGURE ¹⁸). These
structurally related growth factors bind to corresponding nonsignaling membrane coreceptors, GDNF family receptor alpha (GFRA) 1 to 4. Each ligand binds preferentially, but not exclusively, to a distinct GFRA coreceptor. The GDNF ligands and GFRA coreceptors are expressed in overlapping but different tissue types, endowing each complex with somewhat unique cellular functions.\(^\text{3,18,20}\)

Other than not binding ligands directly, RET functions as a typical tyrosine kinase receptor. Its activation is initiated when 2 GDNF ligands form a homodimer that binds a pair of GFRA coreceptors. This ligand-coreceptor complex brings together 2 RET molecules, leading to RET autophosphorylation at key tyrosine residues.\(^\text{3,18,20}\)

These phosphorylated tyrosine residues serve as docking sites for adaptor molecules, which subsequently activate downstream signaling pathways, including the MAPK and PI3K/AKT pathways.\(^\text{3,18,20}\)

**RET AS AN ONCOGENIC DRIVER**

**Thyroid Cancer**

Oncogenic alterations in the *RET* gene in the form of gene fusions were first identified in patients with papillary thyroid cancer (PTC).\(^\text{21}\) Current estimates suggest that *RET* fusions occur in 10% to 20% of sporadic PTCs, with the highest incidence in patients who have been exposed to environmental or therapeutic radiation.\(^\text{3,10,22}\)

*RET* gene fusion results from a chromosomal rearrangement or inversion, and the ensuing chimeric protein consists of RET’s C-terminal kinase domain juxtaposed with the N terminus of another protein. This fusion partner commonly contributes a dimerization domain, leading to constitutive activation of RET kinase activity in the absence of any ligand.\(^\text{3,10,22}\) Among patients with PTC, the most frequently observed *RET* fusion partners are *CCDC6* and *NCOA4*.\(^\text{2,3,22}\)

Gain-of-function point mutations in *RET* also have been found in patients with thyroid cancer. Initially linked to multiple endocrine neoplasia 2, an inherited cancer syndrome characterized by a high risk of medullary thyroid cancer (MTC), *RET* mutations subsequently have been identified in 40% to 65% of sporadic MTC cases, in which their presence correlates with more aggressive disease. *RET* mutations can occur at numerous sites in the gene but are seen predominantly within either the extracellular or kinase domain. Most common is the M918T kinase domain mutation, accounting for nearly 70% of sporadic MTC cases.\(^\text{18,21}\)

**NSCLC**

In 2012, *RET* fusions were first identified in NSCLC, and subsequent studies demonstrated a prevalence of approximately 1% to 2%. *RET* fusions are observed primarily, although not exclusively, in patients who lack other driver alterations, such as *EGFR* mutations and *ALK* gene fusions. In terms of structure and oncogenic mechanism, *RET* rearrangements in NSCLC and thyroid cancer are similar; however, the most common fusion partner in NSCLC is the *KIF5B* gene.\(^\text{18,21}\)

*RET* fusions associated with NSCLC are more prevalent in younger patients who have never or rarely smoked and whose tumors have adenocarcinoma histology and are more poorly differentiated.\(^\text{3}\)

**Other Tumor Types**

In recent years, aberrant RET signaling has been identified in a growing number of tumor types beyond thyroid and lung cancers. In an NGS study of 4871 patients with diverse malignancies, *RET* mutations were identified in small numbers of patients with paraganglioma and ovarian, bladder, and colorectal cancers, among others.\(^\text{17}\) In many cases, the functional relevance of *RET* mutations remains to be determined. *RET* fusions also have been identified at low frequencies in cancer types such as salivary gland, ovarian, colorectal, and pancreatic.\(^\text{22}\)

High levels of RET protein expression have been reported in many malignancies, including breast, prostate, and pancreatic cancers. Notably, RET expression occurs in approximately 40% of breast tumors\(^\text{24}\) and has been found to correlate with resistance to endocrine therapy in estrogen receptor–positive breast cancer.\(^\text{22}\)
MULTIKINASE INHIBITORS

Given the key role of aberrant kinases in the development of cancer, a number of multitargeted kinase inhibitors have been developed and approved for the treatment of several cancer types. Some of these drugs include the RET protein among their targets because its kinase domain is similar in sequence and structure to that of other tyrosine kinases.

Cabozantinib is approved as Cometig for the treatment of metastatic MTC (a different dosage form under the brand name Cabometyx is approved for other indications), as is vandetanib (Caprelsa). Meanwhile, sorafenib (Nexavar) and lenvatinib (Lenvima) are approved for the treatment of radioactive iodine–refractory differentiated thyroid cancer (DTC). However, these approvals do not require patients to have RET alterations, and patients were enrolled in the pivotal phase 3 trials that led to FDA approval irrespective of RET mutation status.

Exploratory analyses in the EXAM trial (NCT00704730) demonstrated that cabozantinib was superior to placebo in patients with MTC, with the greatest benefit—in terms of increased overall response rate (ORR), progression-free survival (PFS), and overall survival—in patients with the RET M918T mutation compared with patients with other RET mutations or wild-type RET. In the ZETA trial (NCT00410761) of vandetanib in MTC, subgroup analyses of ORR and PFS produced inconclusive results when patients were stratified by general mutation status. However, similar to what occurred in the EXAM trial, the M918T-positive group derived greater benefit than the M918T-negative group. Neither pivotal trial for lenvatinib or sorafenib in DTC investigated the impact of RET alteration status on patient outcomes.

Multikinase inhibitors have been studied in patients with RET-rearranged NSCLC, and modest efficacy was reported. However, use of these drugs is limited by the development of resistance and significant toxicity, the latter partly resulting from comitant inhibition of VEGFRs.

RXDX-105 is a VEGFR-sparing multikinase inhibitor developed by Ignyta to address this issue. Data from a phase 1 basket trial (NCT01877811) in patients with RET fusion-positive solid tumors were reported. The ORR was 19%, and the majority of treatment-related adverse events (TRAEs) were grade 1 or 2. Roche subsequently acquired Ignyta, however, and development of this drug was discontinued.

The ORRs reported for multikinase inhibitors in RET-altered NSCLC were lower than those observed with more specific kinase inhibitors in patients with NSCLC driven by other oncogenes, prompting a search for more selective RET inhibitors with greater potency and reduced toxicity.

Two such drugs, pralsetinib and selpercatinib, rapidly advanced through clinical trials and recently received FDA approval for the treatment of RET fusion–positive NSCLC; RET-mutant MTC; and RET fusion–positive, radioactive iodine–refractory thyroid cancer.

FIRST-IN-CLASS SELPERCATINIB

Accelerated approval of selpercatinib was based on the ongoing, open-label, phase 1/2 LIBRETTO-001 trial (NCT03157128) conducted at 65 centers across 12 countries. In the phase 1 dose-escalation portion, patients received doses of selpercatinib ranging from 20 mg once daily to 240 mg twice daily, and in the phase 2 dose expansion, they were treated with 160 mg twice daily. Results from the trial were recently reported, with separate publications detailing outcomes for 2 different patient groups.

Of 144 patients with RET fusion–positive advanced NSCLC who received selpercatinib, 105 were previously treated (49 in dose escalation and 56 in dose expansion; median of 3 prior lines of systemic therapy) and 39 were treatment naïve.

The ORR in previously treated patients was 64% (95% CI, 54%-73%), including 2 complete responses (CRs) and 65 partial responses (PRs). An additional 30 patients achieved stable disease. Responses were observed regardless of the type of prior therapy received. Median duration of response (DOR) was 17.5 months (95% CI, 12 months–not evaluable [NE]), with 63% (95% CI, 42%-67%) of responses ongoing at a median follow-up of 12.1 months. One-year PFS was 66% (95% CI, 55%-74%), and median PFS was 16.5 months (95% CI, 13.7 months–NE).

Notably, among 11 previously treated patients with measurable central nervous system (CNS) metastases at baseline, the intracranial ORR was 91% (95% CI, 59%-100), including 3 CRs and 7 PRs, and median CNS DOR was 10.1 months (95% CI, 6.7 months–NE).

The ORR in treatment-naïve patients was 85% (95% CI, 70%-94%), with 90% of responses ongoing at 6 months, and neither median DOR nor median PFS had been reached at a median follow-up of 7.4 and 9.2 months, respectively.

The second LIBRETTO-001 report described findings for 162 patients with thyroid cancer who were treated across 3 cohorts. In the first cohort, 55 patients with RET-mutant MTC previously treated with cabozantinib and/or vandetanib had an ORR of 69% (95% CI, 55%-81%), including 5 CRs and 33 PRs. Responses were observed in patients with various types of RET mutations, including gatekeeper mutations at residue V804 that confer resistance to multikinase inhibitors. At 1 year, 86% (95% CI, 67%-95%) of responses were ongoing, and 1-year PFS was 82% (95% CI, 69%-90%).

In the second cohort, 88 patients with RET-mutant MTC not previously treated with cabozantinib or vandetanib achieved an ORR of 73% (95% CI, 62%-82%), including 10 CRs and 54 PRs, across patients with various types of RET mutations. At 1 year, 91% (95% CI, 72%-97%) of responses were ongoing, and 1-year PFS was 92% (95% CI, 82%-97%).

Patients with RET fusion–positive thyroid cancer (n = 19), 15 of whom had received prior treatment with multikinase inhibitors, were enrolled in cohort 3. This cohort’s ORR was 79% (95% CI, 54%-94%), with activity observed across multiple thyroid cancer subtypes. At 1 year, 71% (95% CI, 39%-88%) of responses were ongoing and 1-year PFS rate was 64% (95% CI, 37%-82%).
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Among 531 patients who received selpercatinib, 94% experienced any-grade TRAEs, including dry mouth, hypertension, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and fatigue. The most common grade 3/4 TRAEs were hypertension (14%), increased ALT (13%) increased AST (10%), hyponatremia (6%), and lymphopenia (6%). TRAEs led to dose reduction in 30% of patients and treatment discontinuation in 2%.12,13

Phase 3 randomized trials of selpercatinib in RET-mutant MTC and RET fusion-positive NSCLC are ongoing, along with a number of earlier-phase studies. Notably, RET fusions have been reported to be a mechanism of acquired resistance to third-generation EGFR inhibitors in EGFR-mutant NSCLC. This resistance may be overcome by combined RET/EGFR inhibition, which is the rationale for including of selpercatinib in the ongoing phase 2 ORCHARD trial (NCT03944772).

**Pralsetinib and Beyond**

The FDA granted accelerated approvals for pralsetinib based on findings from the ongoing phase 1/2 ARROW trial (NCT03037385), which is being conducted at 75 sites in 11 countries and enrolling patients in 3 cohorts: RET fusion-positive NSCLC, RET-mutant MTC, and other RET fusion-positive tumors. Phase 1 dose escalation has been completed and investigators identified a recommended phase 2 dose of 400 mg once daily. As of February 2020, 438 patients had received treatment over a median follow-up of 8.8 months.10,11,14

The NSCLC indication is based on an ORR of 57% (95% CI, 46%-68%) among 87 patients previously treated with platinum chemotherapy, including a 5.7% CR rate and a 52% PR rate, and an ORR of 70% among 27 patients with treatment-naïve metastatic disease, including an 11% CR rate and a 59% PR rate. The median DOR was not reached in the previously treated cohort (95% CI, 15.2-NE) and was 9.0 months (95% CI, 6.6-NE) in the treatment-naïve group.10

Intracranial responses also were observed among 8 patients with previously treated RET fusion–positive NSCLC who had measurable CNS metastases at baseline. Four of these patients had responses in intracranial lesions, including 2 with a CNS CR.10

In December 2020, the FDA expanded pralsetinib’s approved indications to include patients with RET-mutant MTC and RET fusion–positive thyroid cancer based on response data from ARROW.14 Among 55 patients with RET-mutant MTC previously treated with cabozantinib or vandetanib, the ORR was 60% (95% CI, 46%-73%), including a 1.8% CR rate and a 58% PR rate. In 29 patients with RET-mutant MTC who had not been treated with those drugs, the ORR was 66% (95% CI, 46%-82%), with a 10% CR rate and a 55% PR rate. The median DOR was not reached in either group. In RET fusion–positive thyroid cancer, the ORR in 9 patients was 89% (95% CI, 52%-100%), all PRs, and the median DOR was not reached (95% CI, NE-NE).10

Across all patient cohorts, pralsetinib was well tolerated; most TRAEs were grade 1 or 2, including increased AST, increased ALT, anemia, constipation, and hypertension, and 4% of patients discontinued treatment due to TRAEs.11,14

The FDA approved the Oncomine Dx Target Test (Life Technologies Corporation), an NGS-based test, as a companion diagnostic for the detection of RET fusions to guide the use of pralsetinib in NSCLC. Currently, there is no FDA-approved companion diagnostic for selpercatinib.8,9

Although selective RET inhibitors have demonstrated activity in tumors with RET mutations that confer resistance to multikinase inhibitors, investigators have identified mutations in the solvent front region of the RET protein (at residue G810) that may drive resistance to pralsetinib and selpercatinib.15

Turning Point Therapeutics has developed TPX-0046, which potently inhibits RET in addition to the SRC kinase. TPX-0046 is designed to target the active RET conformation; in a preclinical study, the agent was active in RET-driven cell- and patient-derived tumor xenograft models harboring a wide range of RET alterations, including solvent front mutations.16 A phase 1/2 trial in patients with RET-altered advanced solid tumors is ongoing (NCT04161391).
Systemic Treatment Options Expand in Nonmetastatic NSCLC

by CHRISTINA T. LOGUIDICE

APPROXIMATELY 85% OF ALL lung cancer diagnoses are categorized as non-small cell lung cancers (NSCLCs), which can include adenocarcinomas, large cell carcinomas, and squamous cell carcinomas.1 Although advances in diagnosis and treatment have led to improvements in overall survival (OS) for patients with NSCLC, low rates of survival outcomes are present even in those with nonmetastatic disease, with 54% with stage I, 35% with stage II, 10% to 15% with stage IIIA, and less than 5% with stage IIIB disease alive at 5 years.2 Subsequently, there has been a push to improve treatment for patients with nonmetastatic NSCLC—a setting where cure is far more likely—by better tailoring treatment to fit patients’ tumor profile, disease stage, and situation. “Once patients develop metastatic disease, treatment is not given with the intent of cure,” Jarushka Naidoo, MBCh, MHS, said during a recent OncLive Peer Exchange®. “But we know that in the [nonmetastatic] setting, this is the goal. Let’s face it, that is the most meaningful, the most powerful goal we can ever achieve as cancer specialists.”

A panel of lung cancer experts convened from the United States and Europe to discuss several important studies presented during the European Society for Medical Oncology (ESMO) Virtual Congress 2020 that seek to address the unmet need in treating nonmetastatic NSCLC.

ADAURA: ADJUVANT TKI FOR EARLY-STAGE EGFRL M UTATION–POSITIVE NSCLC

ADAURA (NCT02511106) is a double-blind, phase 3 trial that randomly assigned 682 patients with completely resected EGFR mutation–positive stage IB to IIIA NSCLC 1:1 to receive the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib (Tagrisso) 80 mg orally once daily (n = 339) or placebo (n = 343) for 3 years.3 The primary end point was disease-free survival (DFS) in patients with stage II to IIIA disease per investigator assessment. Secondary end points included DFS in the overall patient population (stage IB to IIIA), OS, and safety.

The simple design of the trial and early discontinuation rates because of the efficacy observed in the investigational arm, which prevented OS data from being collected, were the cause of some concern for the panelists, however, the data may prove to be practice changing and they expressed readiness to adopt osimertinib for their patients with early-stage EGFR-mutated NSCLC. “Obviously, we’d love to have OS results,” Ticiana A. Leal, MD, said, noting that these results were still meaningful. “[OS] is the gold standard. If we’re not going to get that data, I’ll take DFS...with approval on the DFS end point.”

The FDA drew the same conclusion, and on December 18, 2020, the agency approved osimertinib as an adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.4 Osimertinib was previously approved for treatment-naïve patients with metastatic NSCLC harboring these same mutations.
mutations as well as for those with metastatic EGFR T790M mutation-positive NSCLC that has progressed on or after EGFR TKI therapy. When deciding whether to use osimertinib in the adjuvant setting or wait until relapse, Naidoo said her inclination would be to use it as soon as possible. “If we have a shot at cure, therein lie the reasons why many would be open to the use of adjuvant osimertinib, even with an end point that isn’t necessarily considered the gold standard,” she said.

ADAURA showed significant difference in DFS between the osimertinib- and placebo-treated patients well before the study’s planned 3-year mark. At 24 months, 90% of the patients with stage II to IIIA disease in the osimertinib group and 44% of those in the placebo group were alive and free of disease (HR for disease recurrence or death, 0.17; 99.06% CI, 0.11-0.26; P < .001). In the overall patient population, 89% in the osimertinib group and 52% in the placebo group were alive and disease-free at 24 months (HR for disease recurrence or death, 0.20; 99.12% CI, 0.14-0.30; P < .001).

The panelists noted that a common challenge in patients with certain lung cancers is their high risk of central nervous system (CNS) involvement (SNAPSHOT, TABLE 1). “Brain metastases are a common outcome in patients with oncogene-addicted lung cancers—EGFR-mutant lung cancers and others. Patients can be very symptomatic. This can be a difficult complication of this disease. It is difficult to manage,” Naidoo said. She noted that a presentation at ESMO 2020 looked at the CNS disease recurrence data from ADAURA, an exploratory end point within the study.

“We very interestingly, 45 patients had CNS events. Only 6 events were noted in the osimertinib arm compared with 39 events in the placebo arm. The median CNS DFS was not reached. It was 48.2 months for the placebo arm, and a very impressive Kaplan-Meier curve of the CNS DFS presented showed that the osimertinib arm nearly looked parallel, with a hazard ratio of 0.18. The idea that one could actually prevent CNS disease from occurring with adjuvant osimertinib is clinically important,” she said.

Although these data are encouraging, Naidoo indicated that there are some limitations that challenge their interpretation. Of importance, she said not all patients were required to have baseline imaging, making it unclear what their status was before treatment, and that imaging during the study could be computed tomography (CT) or magnetic resonance imaging (MRI). “As we know, CTs of the brain may miss about 10% of brain metastases compared with MRIs of the brain,” she explained. Despite these issues, she said the data were nevertheless “very impressive.”

With biomarker-driven treatments now approved for and showing benefit in nonmetastatic NSCLC, the panelists discussed the role of next-generation sequencing (NGS) for patients with these tumors. “I strongly believe that we should test everyone. This is really important if it can help us make a clinical decision—if we can make a potential predictive value,” Ravi Salgia, MD, PhD, said. The other panelists agreed and noted that information on concomitant mutations that NGS testing yields can further guide therapy, though the information sometimes adds challenges because a lot of questions remain on how some mutations may impact treatment, especially when they occur in certain combinations, and what their presence might mean for treatment sequencing.

Moderator Benjamin P. Levy, MD, provided one such real-world example. “I have a patient with resected ALK lung cancer. Should I be using alectinib [Alecensa] or osimertinib for EGFR? Again, we have a high rate of relapse. We have a known drug with great activity. Is this where we stop and pause or is there a role for adjuvant targeted therapies for other genotypes in the absence of data?” he asked.

CONTINUED ON PAGE 84 ➤
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The panelists used this opportunity to recommend that such patients be considered for the ongoing ALCHEMIST trial (NCT02194738), which is assessing whether adding targeted therapy based on patients’ tumor genetics will prevent cancer recurrence and improve OS. “This is an opportunity where we’re testing patients more commonly in the resected phase, and we can boost accrual to trials like ALCHEMIST,” Leal said.

“The partial response rate was 8.7%, with a major pathologic response rate of 18.6%... the response is higher as the issue was [the trial] was stopped early because 9% [n = 4] had observed deaths,” Salgia said. He noted that these deaths were “most likely not related to the immune checkpoint inhibition but to comorbid disease.” The study authors similarly stated that patients’ comorbidities contributed to postoperative complications, rather than durvalumab exposure causing any life-threatening toxicities. The comorbidities observed in these patients included arterial hypertension, severe chronic obstructive pulmonary disease, diabetes mellitus, ischemic heart disease, and peripheral arterial disease. Overall, durvalumab was well tolerated, with no grade 3 to 5 adverse effects (AEs) observed.

In the PRINCEPS trial, 30 patients received 1 injection of atezolizumab and underwent surgery 4 weeks later. Use of atezolizumab did not impair surgery, and 4 patients (14%) had a major pathological response. Pathological responses did not correlate with RECIST 1.1 response rate or metabolic variations but were found to correlate with high PD-L1 expression. Again, treatment was generally well tolerated and there were no grade 4 or 5 AEs.

“My take-home message is that we’re seeing a similar trend [in neoadjuvant trials] like what we’ve seen in the metastatic setting; single-agent immunotherapy has some response, but it’s pretty limited.”

—JUN ZHANG, MD, PhD

IFCT-1601 IONESCO AND PRINCEPES TRIALS: NEOADJUVANT IMMUNOTHERAPY FOR EARLY-STAGE NSCLC

IFCT-1601 IONESCO (NCT03030131) and PRINCEPES (NCT02994576) assessed the PD-L1 inhibitors durvalumab (Imfinzi) and atezolizumab (Tecentriq), respectively, as neoadjuvant treatment options for patients with early-stage NSCLC. Somewhat disappointingly to the panelists, both demonstrated slightly less promising activity than earlier immunotherapy trials in this space.

In the IONESCO study, durvalumab was given on days 1, 15, and 29, with surgery undertaken 2 to 14 days after the last infusion. Among the 46 included patients, 41 (89.1%) had a complete resection, 2 (4.3%) had a microscopically incomplete resection, and 3 (6.5%) did not undergo surgery. The partial response rate was 8.7%, with a major pathologic response rate of 18.6%. The issue was that the trial was stopped early because 9% [n = 4] had observed deaths,” Salgia said. He noted that these deaths were “most likely not related to the immune checkpoint inhibition but to comorbid disease.” The study authors similarly stated that patients’ comorbidities contributed to postoperative complications, rather than durvalumab exposure causing any life-threatening toxicities. The comorbidities observed in these patients included arterial hypertension, severe chronic obstructive pulmonary disease, diabetes mellitus, ischemic heart disease, and peripheral arterial disease. Overall, durvalumab was well tolerated, with no grade 3 to 5 adverse effects (AEs) observed.

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“My take-home message is that we’re seeing a similar trend like what we’ve seen in the metastatic setting. Single-agent immunotherapy has some response, but it’s pretty limited. When we combine that with chemotherapy, the response is higher, especially when we use the major pathologic response. When we combine with another IO [immuno-oncology] therapy—IO plus IO—it seems like the response is higher as well,” Jun Zhang, MD, PhD, said. Subsequently, he said he would probably favor exploring such approaches over monotherapy in the neoadjuvant setting but emphasized that caution is warranted because other trials have shown an increase in toxicities with combination approaches in this setting. As an example, he used the NADIM trial (NCT03081689), which assessed neoadjuvant paclitaxel, carboplatin, and nivolumab. In the study, 14 of 46 patients (30%) experienced grade 3 or higher treatment-related AEs. “Whether [such toxicities] would really delay surgery in the real world is another question,” he said.

Salgia noted that cases of hyperprogression have also been observed in patients receiving immune checkpoint inhibitor and chemotherapy combinations. “We have to really consider whether we should do NGS on those patients up front to see if there’s a negative predictor, such as STK11 or MDM2 or something else, that will help us prevent that,” he said. Zhang agreed, noting that while the risk of hyperprogression occurring in clinical trials is rare, “we cannot really afford for any patient in our lives to get to hyperprogression.”

PACIFIC TRIAL: IMMUNOTHERAPY AFTER CHEMORADIOThERAPY FOR UNRESECTABLE STAGE III NSCLC

Finally, the panelists examined data from the PACIFIC trial (NCT02125461), which led to the FDA’s approval of durvalumab in 2018 for patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. The PACIFIC trial randomly assigned 713 patients in a 2:1 ratio to durvalumab (n = 473) or matching placebo (n = 236) every 2 weeks for up to 12 months after completion of concurrent chemoradiation with at least 2 cycles of platinum-based chemotherapy. To date, data have shown a benefit in progression-free survival (PFS) and OS. After a median follow-up of 25.2 months, the 24-month OS rate was 66.3% in the durvalumab arm versus 55.6% in the placebo arm (two-sided P = .005), with an HR for death of 0.68 (99.73% CI, 0.47-0.997; P = .0025). The median PFS was 17.2 months in the durvalumab arm and 5.6 months in the placebo arm (stratified HR for disease progression or death, 0.51; 95% CI, 0.41-0.63), whereas the median time to death or distant metastasis was 28.3 months in the durvalumab arm and 16.2 months in the placebo arm (stratified HR, 0.53; 95% CI, 0.41-0.68).

During ESMO 2020, data were presented for the 4-year OS update, which had a median follow-up of 34 months. The good thing about having the updates is that it’s been reassuring to see that the data are holding up, and we’re seeing consistent improvements in PFS over time, as well as OS. This leads us to think that with the 5-year OS update, perhaps we’re actually going to be talking about cure rates,” Leal said.
The updated post-hoc analyses showed an estimated 4-year OS rate of 49.6% in the durvalumab arm versus 36.3% for the placebo arm after chemoradiotherapy. The median OS was 47.5 months for durvalumab versus 29.1 months for placebo. With a maximum treatment course of 1 year, an estimated 35.3% of patients treated with durvalumab had not progressed 4 years after enrollment versus 19.5% for placebo. “These are really impressive results. The tolerability of durvalumab has been well known to all of us, and it is well demonstrated in the trial. It really is a game changer,” Leal said.

Because the PACIFIC trial did not allow consolidation chemotherapy and one-third of patients received induction chemotherapy, which might not reflect real-life practice, Levy asked the panelists how they are putting the data into clinical practice, including which chemosensitization regimens they are using and whether they always start durvalumab right after radiation treatment is completed or give consolidation treatment.

Leal said that she may alter treatment in certain situations, including for those with severe neuropathy who cannot handle paclitaxel. “I want to make sure we don’t rock the boat during chemoradiation with extra toxicity. In general, I’ve preferred to use the carboplatin-paclitaxel regimen on a weekly basis during radiation.” As for consolidation chemotherapy, she said she has gotten away from using it. “We did that in select patients because we had intuitively thought that more is better. But, really, we have not seen that pan out in phase 3 clinical trials. So I don’t use consolidation chemotherapy. I am happy to let that go, and so are patients. That added toxicity might take patients away from being able to get to the consolidation with durvalumab, which is really the main goal,” she said.

Naidoo said she uses carboplatin-paclitaxel for many patients, but she also uses platinum-pemetrexed for those with adenocarcinoma because it is very well tolerated. “In terms of the timing of beginning durvalumab, a change in the protocol to allow for a wider window in commencing treatment changed our paradigm slightly, in requiring a scan to rule out progression. Beforehand, this was something we weren’t necessarily doing until later. The timing has become more of an issue and requires us to have seamless communication with our radiation oncology colleagues. That might change the workflow for many oncologists in settings where they don’t have real-time access to their radiation oncologists,” she said.

Salgia noted that a key issue will be determining what kind of durvalumab dosing and duration are truly needed to optimize outcomes while reducing toxicity risks. Currently, patients weighing at least 30 kg can receive durvalumab 10 mg/kg every 2 weeks or 1500 mg every 4 weeks, whereas those weighing less than 30 kg must receive the weight-based dosing. It is also unclear whether 1 year of treatment like in the PACIFIC trial is ideal or whether a shorter treatment course would yield comparable results or a longer treatment course would be superior in improving outcomes. “Those are all important questions as we go forward. But this is 1 of the first landmark studies that has revolutionized our practice,” he said.

### TABLE 2. 4-Year Survival Update From the PACIFIC Trial

<table>
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<th>Outcome</th>
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<td>29.1</td>
</tr>
<tr>
<td>48-month OS rate</td>
<td>49.6%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>17.2 (HR, 0.55; 95% CI, 0.44-0.67)</td>
<td>5.6</td>
</tr>
<tr>
<td>48-month PFS rate</td>
<td>35.3%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival.

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**REFERENCES**

Clonal evolution is a root cause of treatment resistance in multiple myeloma that may ultimately result in triple-class refractory (TCR) disease. Patients are considered TCR when they are resistant to ≥1 treatment in all 3 standard-of-care classes (proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies).1-4

Peptide-drug conjugates and antibody-drug conjugates represent a strategy designed to deliver a cytotoxic agent directly into tumor cells.5

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